U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
PB80-131428

Potential Atmospheric Carcinogens Phase 1. Identification and Classification

Monsanto Research Corp, Dayton, OH Dayton Lab

Prepared for

Environmental Sciences Research Lab, Research Triangle Park, NC

Jan 80

United States
Environmental Protection
Agency

Environmental Sciences Research
Laboratory
Research Triangle Park NC 27711

EPA-600/2-80-015
January 1980

Research and Development

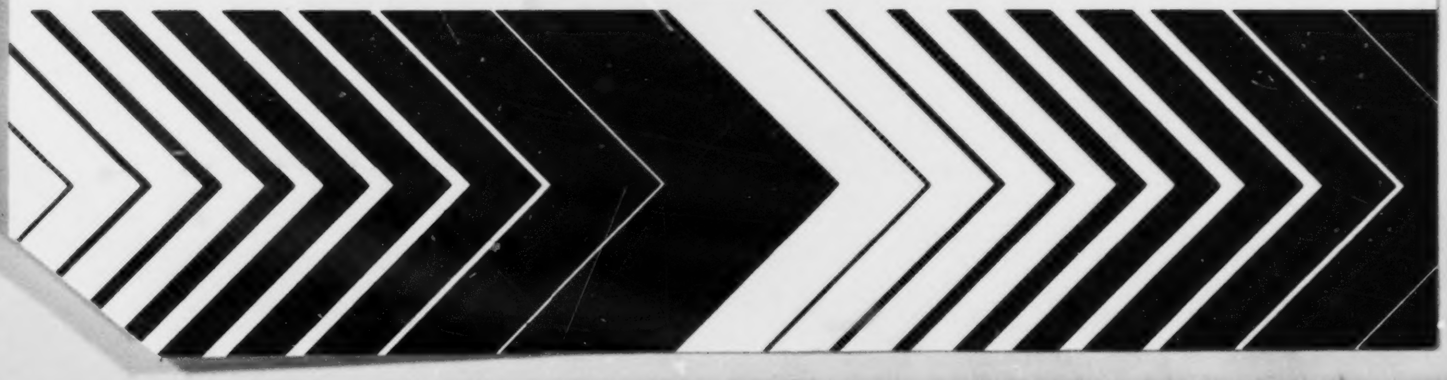
PB80-131428

EPA

Potential Atmospheric Carcinogens

Phase 1
Identification and Classification

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161



RESEARCH REPORTING SERIES

Research reports of the Office of Research and Development, U.S. Environmental Protection Agency, have been grouped into nine series. These nine broad categories were established to facilitate further development and application of environmental technology. Elimination of traditional grouping was consciously planned to foster technology transfer and a maximum interface in related fields. The nine series are:

1. Environmental Health Effects Research
2. Environmental Protection Technology
3. Ecological Research
4. Environmental Monitoring
5. Socioeconomic Environmental Studies
6. Scientific and Technical Assessment Reports (STAR)
7. Interagency Energy-Environment Research and Development
8. "Special" Reports
9. Miscellaneous Reports

This report has been assigned to the ENVIRONMENTAL PROTECTION TECHNOLOGY series. This series describes research performed to develop and demonstrate instrumentation, equipment, and methodology to repair or prevent environmental degradation from point and non-point sources of pollution. This work provides the new or improved technology required for the control and treatment of pollution sources to meet environmental quality standards.

This document is available to the public through the National Technical Information Service, Springfield, Virginia 22161.

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/2-80-015	2.	3. RECIPIENT'S ACCESSION NO. PB80-131428
4. TITLE AND SUBTITLE POTENTIAL ATMOSPHERIC CARCINOGENS Phase 1. Identification and Classification		5. REPORT DATE January 1980
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Carl R. McMillin, Leland B. Mote, and Daryl G. DeAngelis		8. PERFORMING ORGANIZATION REPORT NO. MRC-DA-870
9. PERFORMING ORGANIZATION NAME AND ADDRESS Monsanto Research Corporation Dayton Laboratory 1515 Nicholas Road, P.O. Box 8, Station B Dayton, Ohio 45407		10. PROGRAM ELEMENT NO. 1HE775D CB-005 (FY-79)
		11. CONTRACT/GRANT NO. 68-02-2773
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Sciences Research Laboratory -- RTP, NC Office of Research and Development U. S. Environmental Protection Agency Research Triangle Park, North Carolina 27711		13. TYPE OF REPORT AND PERIOD COVERED Interim 9/77 - 10/78
		14. SPONSORING AGENCY CODE EPA/600/09

15. SUPPLEMENTARY NOTES

16. ABSTRACT

A comprehensive literature search identified more than 125 high-volume chemicals having the potential of becoming airborne carcinogenic pollutants. Based on carcinogenicity and mutagenicity data, the pollutants were divided into three categories: probable carcinogens, possible carcinogens, and probable noncarcinogens. Additional data were collected for the possible and probable carcinogens including their annual production, emissions, atmospheric persistence, and relative mutagenic and carcinogenic potencies. The pollutants were then ranked on the basis of a calculated equivalent weight of benzo(a) pyrene emitted per year after 24 hours in the atmosphere. From the top portions of these two lists, 20 compounds, representing various chemical classes, were chosen for future analysis. A state-of-the-art review of the effect of cofactors on the carcinogenicity of chemicals was also completed. To locate optimum sampling sites in cities of interest, a series of carcinogen isopleths was generated. Using information such as the locations of stationary sources of carcinogenic pollutants, normalized wind direction and speed, and the height, temperature, and rate of flow of the sources, the probable locations of maximum carcinogenic pollution concentration were computed.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
*Air pollution		13B
*Carcinogens		06E
*Reviews		05B
*Identifying		

18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS *(This Report)* UNCLASSIFIED	21. NO. OF PAGES 255
	20. SECURITY CLASS *(This page)* UNCLASSIFIED	22. PRICE A12-A01

EPA Form 2220-1 (9-73)

EPA-600/2-80-015
January 1980

POTENTIAL ATMOSPHERIC CARCINOGENS
Phase 1. Identification and Classification

by

C. R. McMillin, L. B. Mote,
and D. G. DeAngelis
Monsanto Research Corporation
Dayton, Ohio 45407

Contract No. 68-02-2773

Project Officer

James Mulik
Atmospheric Chemistry and Physics Division
Environmental Sciences Research Laboratory
Research Triangle Park, North Carolina 27711

ENVIRONMENTAL SCIENCES RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NORTH CAROLINA 27711

DISCLAIMER

This report has been reviewed by the Environmental Services Research Laboratory, RTP, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

ABSTRACT

On the basis of a comprehensive literature search, 20 significant atmospheric carcinogens were identified from more than 125 high-volume chemicals having the potential of becoming airborn pollutants. The pollutants were divided into probable carcinogens (substantial data indicating carcinogenicity, generally including positive animal studies), possible carcinogens (positive mutagenicity results from at least one fairly well-established test or from several less established tests), and probable noncarcinogens (negative results on the bulk of the tests which had been conducted). These evaluations are presented along with all of the references used to make the determinations.

Additional data were collected for the possible and probable carcinogens including their annual production, emissions, atmospheric persistence, and relative mutagenic and carcinogenic potencies. The pollutants were then ranked based on a benzo(a)-pyrene equivalent (potency) annually emitted remaining after 24 hours in the environment. From the top portions of these 2 lists, 20 significant carcinogens were chosen for future analysis, avoiding closely similar chemical types. A state-of-the-art review of the effect of cofactors on the carcinogenicity of chemicals was also completed in the first phase of this research.

To locate optimum sampling sites in cities of interest, a series of carcinogen isopleths was generated. The locations of stationary sources of carcinogenic pollutants were first determined. Using information such as the normalized wind direction and speed, and the height, temperature, and rate of flow of the sources, the probable locations of maximum carcinogenic pollution concentration were computed.

This report was submitted in partial fulfillment of Contract No. 68-02-2773 by Monsanto Research Corporation under the sponsorship of the U.S. Environmental Protection Agency. The report covers the period 29 September 1977 to 31 October 1978, and work was completed as of December 1978.

CONTENTS

Abstract . . . iii
Figures . . . vi
Tables . . . vi

1. Introduction . . . 1
2. Conclusions . . . 3
3. Recommendations . . . 5
4. Selection of 20 Significant Atmospheric Carcinogens . . . 6
    - Carcinogens selection of candidate chemicals . . . 6
    - Evaluation of carcinogenicity . . . 11
    - Summary report on the review of the carcinogens literature . . . 13
    - Production of possible and probable carcinogens . . . 14
    - Emission of possible and probable carcinogens . . . 14
    - Atmospheric persistence of possible and probable carcinogens . . . 14
    - Potency of possible and probable carcinogens . . . 24
    - Relative mutagenic potency . . . 27
    - Relative carcinogenic potency . . . 27
    - Prioritization of possible and probable carcinogens . . . 27
5. State-of-the-Art Review of Carcinogenic Cofactors . . . 32
6. Carcinogen Isopleth Generation . . . 33

References . . . 47
Appendices

A. Review of the carcinogen literature of 125 chemicals . . . 82
B. Review of the carcinogen cofactor literature . . . 217

Preceding page blank

FIGURES

Number Page

1 Ethylene Dichloride Concentrations in Houston, Texas at 500 μg/m³ (3 km/cm) 31
2 Input Data 32
3 Output Data 36
4 Houston Carcinogen Isopleth 40
5 Locations of Maximum Concentration of Pollutants in Houston 41

TABLES

1 Preliminary List of Candidate Carcinogens 3
2 Sources for Selection of Candidate Chemicals 7
3 Additional Production Figures 10
4 Production-Ranked Probable Carcinogens 12
5 Production-Ranked Possible Carcinogens 13
6 Emissions-Ranked Probable Carcinogens 15
7 Emissions-Ranked Possible Carginogens 16
8 Emissions/Persistent-Ranked Probable Carcinogens 17
9 Emissions/Persistence-Ranked Possible Carcinogens 18
10 Relative Mutagenic Potency 20
11 Preliminary Mutagenic Potency Data 21
12 Other Mutagen Data to Consider 21
13 Relative Mutagenic/Carcinogenic Potency of Probable Carcinogens 23
14 Relative Mutagenic/Carcinogenic Potency of Possible Carcinogens 24
15 Ranking of Probable Carcinogens by Equivalent Emissions of B(a)P After 24 Hours 25
16 Ranking of Possible Carcinogens by Equivalent Emissions of B(a)P After 24 Hours 26
17 Chemicals in Top 30 Probable Carcinogens on MRC Data Base That Are Found in Four Cities 29
18 Average Concentrations at Points of Maximum Pollution in Houston 40

SECTION 1

INTRODUCTION

The growing recognition that exposure to certain substances in the environment may pose health hazards has prompted a critical examination of the available screening procedures and analytical methodology for reliable monitoring. Although the U. S. Environmental Protection Agency (EPA) is generally concerned with a wide range of pollutants, the pollutants or hazardous materials that are also carcinogenic have been assigned a high priority owing to their adverse effects on public health.

The objective of this research was to develop sampling and analytical techniques and instrumentation for 15 of the most significant atmospheric carcinogens and field validate the technology which is developed. In the first phase of this research several tasks were completed, including (1) the identification of 20 significant atmospheric carcinogens from which the EPA was to select 15 pollutants for study; (2) the collection of information pertaining to the effects of cofactors, inhibitors, promoters, etc., on carcinogens; (3) and the generation of carcinogen isopheths to locate optimum sampling sites in the cities to be used for field validation of the developed technology.

In order to select these 20 significant atmospheric carcinogens, Monsanto Research Corporation (MRC) first selected a number of candidate chemicals having the potential of becoming atmospheric pollutants which are produced in fairly high volume and have been cited in the literature as being carcinogens or portential carcinogens. The primary (original) literature was consulted to see whether it indicated that the chemicals were carcinogenic. The chemicals were then classed as either probable carcinogens, possible carcinogens, or probable noncarcinogens. Production figures, emission figures, environmental persistence data, and potency data were then assembled in order to prioritize the chemicals. Twenty pollutants representing a variety of chemical types were then selected from the most significant possible and probable carcinogens.

One complication to the carcinogenic effect of materials considered in this project is the possible synergistic effects of other materials on the chosen carcinogens. It is well established that other materials can act as cofactors and either enhance or inhibit the effects of a known carcinogen. Often, however, there is not agreement in the literature as to the precise nature of the synergistic effects or which materials have this property. A comprehensive literature search on the state of the art of carcinogenic cofactors therefore was conducted. This search and the resulting review concentrated on the effects of various industrial chemicals on the carcinogenic potential of other industrial chemicals. It also lightly covered other cofactor effects such as physiological (e.g., hormonal), genetic, medical (e.g., disease states), environmental (e.g., light), dietary, and other factors that affect the initiation or growth of cancers.

A portion of the effort in the first phase of this research was devoted to determining the location of optimum sampling sites in four cities where field validation of the sampling and analysis equipment and techniques is to occur (Houston, Los Angeles, Birmingham, and Newark).

In order to accomplish this task, the MRC Source Assessment Data Base was used to obtain most of the necessary input for the EPA Climatological Dispersion Model (CDM). The chemicals included in the study were from the list of probable chemical carcinogens generated earlier in the project. The carcinogenic isopleths were generated for Houston for inclusion in this report.

During the remaining two years of this contract, sampling and analytical techniques and instrumentation will be developed for at least 15 of the atmospheric carcinogens selected and a field validation of this methodology will be conducted.

SECTION 2

CONCLUSIONS

An extensive review of the primary carcinogen and mutagen literature of more than 125 chemicals having the potential of becoming atmospheric pollutants was conducted. It was determined that for 38 of these chemicals there is a substantial amount of information confirming either that they are carcinogenic or that they have been regulated as a carcinogen. These chemicals usually had both positive animal studies and mutagenicity tests. Another 28 chemicals were determined to be possible carcinogens. For these chemicals, one or more significant mutagen tests were reported to be positive but carcinogen results were ambiguous if they had been conducted. The remaining chemicals had been labeled potential carcinogens in this literature at some point. However, a careful review of the presently available literature indicates that they are probably non-carcinogenic.

Information was gathered on the 66 possible and probable carcinogens so that a prioritization model could be used to determine the most significant atmospheric pollutants. Production volumes, emission factors, atmospheric half-life values, mutagenic potency, and carcinogenic potency were considered in determining the significance of the pollutants. A final ranking was made for both the possible and probable carcinogens based upon the equivalent kilograms of benzo(a)pyrene emitted per year remaining after 24 hours in the atmosphere.

From these two ranked lists, 20 pollutants were selected which represented a variety of chemical types and were high in the prioritized ranking. These chemicals are as follows: benzo(a)-pyrene, tetrachloroethylene, ethylene dichloride, benzene, carbon tetrachloride, ethylene dibromide, toluene-2,4-diamine, dioxane, acrylonitrile, chrysene, benzyl chloride, benzidine, pentachlorophenol, dichloropropene, styrene, hexachlorobutadiene, di-(2-ethylhexyl) phthalate, vinyl acetate, ethylene oxide, and acrolein.

A review of more than 2,300 literature citations of the carcinogens cofactor literature was completed. This review includes sections on dietary cofactors, physical agents and body materials, therapeutic agents and treatments, environmental cofactors, industrial chemicals and pollutants, and esoteric materials and other substances. The development of cancer in laboratory animals and humans is a complicated process which may be enhanced or inhibited by a wide variety of conditions. Probably the most significant cofactor is smoking. Smoking exposes individuals not only to carcinogenic substances but also has been demonstrated to increase the risk of personnel exposed to agents such as asbestos and radiation.

A series of isopleths were generated for Houston which illustrate that there are three locations in that city with approximately the same total average carcinogenic pollution burden. The burden at the first location is almost totally due to benzene with a minor component of ethylene dichloride. The burden at the other two locations primarily comprise ethylene dichloride with significant amounts of carbon tetrachloride and chloroform and lesser amounts of trichloroethylene and vinyl chloride. A model of the isopleths illustrates the importance of properly selecting the sampling sites.

SECTION 3

RECOMMENDATIONS

It is recommended that 15 chemicals be selected by EPA for use in this research from among the 20 chemicals listed in the Conclusions section. These chemicals will be the target pollutants for the research on sampler development and analytical technique development. With the prioritization model devised for this research, the relative significance of any other chemicals or pollutants of interest can easily be determined.

A large number of varied influences affect the development of cancer in humans and animals. With the exception of smoking, which is clearly an important carcinogenic cofactor, the significance of many of these cofactors has yet to be demonstrated.

From the carcinogen isopleths generated for Houston, it is readily apparent that the sampling location selected greatly influences the quantity and composition of the pollutants being monitored. Since a greater variety of pollutants can be found at the second and third of the three locations examined, it is recommended that one of these locations be used for the field validation of the sampler for this contract and for contract 68-02-2774, using the portable carcinogen sampler.

SECTION 4

SELECTION OF 20 SIGNIFICANT ATMOSPHERIC CARCINOGENS

The first task required in this contract was to identify 20 significant atmospheric, carcinogenic, pollutant chemicals. In order to select these 20 significant atmospheric carcinogenics, Monsanto Research Corporation (MRC) first selected a number of candidate chemicals which are produced in fairly high volume and have been cited as being a carcinogen or potential carcinogen by some piece of literature. The primary (original) literature was consulted to see whether it indicated that the chemicals were carcinogenic. The chemicals were then classed as either probable carcinogens, possible carcinogens, or probable noncarcinogens. Production figures, emission figures, environmental persistence data, and potency data were then assembled in order to prioritize the chemicals. Twenty chemicals representing a variety of chemical types were then selected from the most significant possible and probable carcinogens.

SELECTION OF CANDIDATE CHEMICALS

The first list of candidate chemicals was obtained by determining which chemicals on the MRC Source Assessment Data Base [1] are also found on the 1976 NIOSH Suspected Carcinogen List [2].

---

[1] Eimutis, E. C., and R. P. Quill. Source Assessment: Noncriteria Pollutant Emissions. EPA-600/2-77-107e (National Technical Information Service No. PB 270 550), 1977.

[2] Suspected Carcinogens - A Subfile of the NIOSH Toxic Substances List, 1976 Edition, H. E. Christensen, ed. Publication No. (NIOSH) 75-188, U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health.

It was determined that 83 compounds on the MRC emissions data base were also on the 1976 NIOSH Suspected Carcinogen List or were cited in the "Registry of Toxic Effects of Chemical Substances" [3] as a mutagen, teratogen, or neoplastic agent. Of these 83, 47 compounds had references indicating positive mutagenic, carcinogenic, teratogenic, or neoplastic test results. The remaining 36 are on the suspected carcinogen list only because of current interest, with citations such as "currently undergoing tests," "candidate for additional oncological information," or "EPA selected for priority attention as point source water effluent discharge toxic pollutant." These two lists of chemicals are shown in Table 1.

Dr. Sawicki's list of atmospheric vapors and gases [4] was checked against the NIOSH list, and materials common to both compilations were found to be present on our list. The 1972-1973 "Survey of Compounds Which Have Been Tested for Carcinogenic Activity" [5] for which positive results were obtained was checked against the source assessment data base. It was found that our preliminary list included all compounds common to both tabulations.

A report entitled "Preliminary Scoring of Organic Air Pollutants" lists 637 organic chemicals along with their production, volatility, and toxicity data [6]. Of these chemicals, 108 are cited as being either mutagenic or carcinogenic, or as producing neoplasms. Subtracting the chemicals already under consideration and the high polymers reduced the number to 74 materials. Eliminating chemicals for which production figures were not available or were less than 455,000 kilograms (1 million pounds) per year produced a list of 20 chemicals to be further evaluated. There are listed below with their annual production.

---

[3] Registry of Toxic Effects of Chemical Substances, Volumes I and II, E. J. Fairchild, ed. DHEW Publication No. (NIOSH) 78-104-A, U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, September 1977.

[4] Sawicki, E. Chemical Composition and Potential "Genotoxic" Aspects of Polluted Atmospheres. In: Air Pollution and Cancer in Man, U. Mohr, D. Schmahl, and L. Tomatis, eds. International Agency for Research on Cancer Scientific Publication No. 16, 1977. pp. 127-157.

[5] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Volumes 1 through 7. DHEW Publication No. (NIH) 75, Public Health Service Publication No. 149, U.S. Department of Health, Education, and Welfare, National Institutes of Health.

[6] Fuller, B., et al. Preliminary Scoring of Selected Organic Air Pollutants. National Technical Information Service Nos. PB 264 442 through PB 264 446, 1976.

TABLE 1. PRELIMINARY LIST OF CANDIDATE CARCINOGENS

	Carcinogenic/neoplastic/ teratogenic/mutagenic compounds	Emissions, metric tons/yr	No. of industry types emitting
1	Trichloroethylene	158,070	5
2	Vinyl chloride	142,290	6
3	Benzene	102,348	15
4	Formaldehyde	40,695	16
5	Maleic anhydride	18,764	3
6	Carbon tetrachloride	12,672	11
7	Chloroprene	7,459	2
8	Methyl ethyl ketone	5,324	2
9	Ethylene oxide	4,540	8
10	Propylene oxide	4,386	2
11	Phenol	4,383	13
12	1,1-Dichloroethane	2,559	2
13	Chloroform	1,069	4
14	Naphthoquinone	1,051	1
15	Ethylene dibromide	886	2
16	Dichlorobutene	866	1
17	Benzo(a)pyrene	830	58
18	Methyl methacrylate	727	1
19	Acrylonitrile	538	4
20	Epichlorchydrin	224	2
21	Hydroquinone	101	1
22	Biphenyl	92	1
23	Naphthalene	90	1
24	Propanol	5	2
25	Parathion	42	1
26	Chloracetic acid	37	3
27	Dichlorophenol	37	3
28	Methylenedianiline	26	1
29	Benzyl chloride	24	1
30	DDT	19	1
31	Polychlorinated biphenyls	18	1
32	Naphthyl methylcarbamate	12	1
33	Quinone	6	1
34	Hydrazine	3	1
35	Endosulfan	2	1
36	Dichloronaphthoquinone	0.9	1
37	Trichlorophenol	0.5	1
38	Methylstyrene	0.5	1
39	Dichlorovinyl dimethyl phosphate	0.2	1
40	Trichlorfon	0.1	1
41	Anthracene	0.1	1
42	Benz(a)anthracene	<0.1	1
43	Bis(chloromethyl) ether	<0.1	1
44	Captan	<0.1	1
45	Diazinon	<0.1	1
46	Nitrosodimethylamine	<0.1	1
47	Pyrene	<0.1	1

(continued)

TABLE 1 (continued)

	Candidates with no references cited	Emissions metric tons/yr	No. of industry types emitting
1	Toluene	331,473	11
2	Trichloroethane	180,128	1
3	Tetrachloroethylene	77,418	4
4	Ethylene dichloride	67,079	10
5	Acetone	29,057	11
6	Methylene chloride	27,138	5
7	Carbon disulfide	25,768	7
8	Methyl chloride	22,944	7
9	Ethanol	11,548	12
10	Acrolein	6,495	4
11	Styrene	5,625	4
12	Vinylidene chloride	1,328	4
13	Dichlorodifluoromethane	425	1
14	Allyl chloride	421	2
15	Dichloroethylene	419	1
16	Trichlorofluoromethane	85	1
17	Aniline	8	3
18	Nitrobenzene	45	3
19	Nitrophenols	11	1
20	Heptachlor	11	1
21	Malathion	10	1
22	Tetrachloroethane	9	1
23	Diphenyl oxide	7	2
24	Methyl bromide	6	1
25	*o*-Dichlorobenzene	3	2
26	*p*-Dichlorobenzene	3	2
27	Kelthane	2	1
28	Endrin	2	1
29	Dinitrotoluene	0.4	1
30	Nitrochlorobenzene	0.3	1
31	Dichloropropionic acid	0.2	1
32	Dursban	0.1	1
33	Ethyl benzene	0.1	1
34	Fluoranthene	<0.1	1
35	Guthion	<0.1	1
36	Toxaphene	<0.1	1

Chemical	Production, kg/yr
Acetaldehyde	680
Aldrin	11
Benzidine	5
Chlorobenzilate	1
Cumene hydroperoxide	900
Di-(2-ethylhexyl) phthalate	180
Dimethylhydrazine	0.5
Disodium methanearsonate	16
Eptam	2
Ethylene glycol	1,700
Ethylenimine	2
Hexamethylenetetramine	46
4,4'-Methylene bis(2-chloroaniline)	3.5
Morpholine	10
Naphtha	3,800
Pentachlorophenol	20
n-Pentane	220
Sorbic acid	18
Tetraethyl lead	160
Toluene-2,4-diamine	29

Of the 80 compounds covered in the report, "Research Program on Hazard Priority Ranking of Manufactured Chemicals" [7], 33 had already been considered. Excluding solids such as polyurethane, high-boiling liquids such as silicone fluids, and low-volume chemicals such as vat blue dye #6 left 16 chemicals to be considered for this project. Three of them (perchloroethylene, vinyltoluene, and 2-mercaptothiazole) were tentatively identified as being noncarcinogens. A fourth, bis(2-chloroethyl) ether, is produced or released in extremely small quantities, if at all. The remaining 12 are as follows:

Hexachlorobenzene
Hexachlorobutadine
Tetrabromoethane
Dichloropropene
Sulfolane
2-Methoxyethanol
4,4-Methylene bis(2-chloroaniline)
Dimethylamine
Dioxane
Ethylenimine
Benzidine
Dichlorobenzidine

---

[7] Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 161, 1975.

"Review of the Environmental Fate of Selected Chemicals" evaluates 74 suspected carcinogens for their environmental persistence. More than 20 of these chemicals were already under consideration. Many of the rest of the chemicals are either produced in low quantities (<455 kg/yr) or are essentially nonvolatile. The remaining chemicals and their production volumes are listed below:

Di-tert-butyl peroxide	1.4×10^6	
Hydrogen peroxide	0.9×10^6	Normal metabolite
1-Naphthylamine	3.2×10^6	
Benzoyl chloride	6.8×10^6	Air 1/2 life = 10 min

A series of reports on 11 compounds prepared by the Office of Air Quality Planning and Standards Department of EPA consists of carcinogenic and mutagenic information for the air pollution assessment of these compounds. Those which were not yet being considered were added to our list.

MRC's Environmental Analytical Sciences Center (EASC) personnel suggested that a few other high-volume chemicals should be considered in this project if they are reported to be carcinogens or mutagens, including:

Chloropropane
Dimethyl acetamide
Vinyl acetate
Vinyl bromide

A summary of the sources of candidate chemicals for investigation in this project is shown in Table 2.

EVALUATION OF CARCINOGENICITY

An attempt was made to obtain primary literature references for each of the chemicals under consideration. A computer information retrieval search was also made for each of the chemicals using both the CANCERLINE and TOXLINE data bases. The primary literature shows on what basis a chemical was added to the NIOSH Suspected Carcinogen List while the CANCERLINE and TOXLINE bases list recent tests run on the compounds and current thoughts on each compound in the published literature.

Based on these sources of data, coupled with information from Reference 5, a qualitative determination was made as to which chemicals are probable carcinogens, possible carcinogens, or probable noncarcinogens for purposes of this project.

Many of these chemicals are currently undergoing carcinogenicity tests. Therefore, these lists represent only an indication of which chemicals will probably be labeled as carcinogens after

TABLE 2. SOURCES FOR SELECTION OF CANDIDATE CHEMICALS

Number of potential candidates	Number of candidates selected	Source
>300	83	MRC Source Assessment Data Base [1] and NIOSH Suspected Carcinogens List [2]
637	20	Preliminary Scoring of Organic Air Pollutants [6] and indicated as a carginogen or mutagen
80	12	Research Program on Hazard Priority Ranking of Manufactured Chemicals [7] and indicated as a mutagen or carcinogen
74	4	Review of the Environmental Fate of Selected Chemicals [8] and production of >455 kg/yr
11	4	Miscellaneous sources
>4	4	Suggested by EASC
>1,106	127	

comprehensive testing is complete. The inclusion of chemicals with so little data is necessary for this project since only a few chemicals have been specifically designated as known human carcinogens.

In the evaluation of carcinogenicity, two of the major problems encountered were lack of data and conflicting data. Maleic anhydride exemplifies the former problem. It is on the NIOSH list because of a 1961 test where two out of three male rats of an unspecified strain developed local sarcomas after repeated injections of maleic anhydride. A check of the current literature did not uncover any other significant tests which have been conducted on maleic anhydride.

Conflicting data exist for formaldehyde. Many reports show formaldehyde as a mutagen and/or a carcinogen in many types of short-term test systems. There are also comments to the effect that humans have repair mechanisms for the damage done by formaldehyde. We therefore decided to consider formaldehyde a possible carcinogen.

---

[8] Radding, S. B., et al. Review of the Environmental Fate of Selected Chemicals. EPA-560/5-77-003 (National Technical Information Service No. PB 267 121), May 1977.

Another problem is that some of the suspected carcinogens have been administered with benzene as the solvent. The solution was to disregard such data if there were sufficient other data available on the compound. If other data were not available, we had to consider whether benzene was carcinogenic by the route of administration, and as a last resort, how potent benzene was by that route of administration.

In addition to the available primary references, general sources of information on the carcinogenicity of chemicals were consulted, such as International Agency for Research on Cancer Monographs and results from National Cancer Institute bioassays.

In the search for information on 127 fairly high-volume chemicals suggested by some type of literature as being carcinogenic, substantiating carcinogenic data were found in the literature for 38. These were labeled probable carcinogens. Information such as mutagenicity data indicated that another 28 chemicals may possibly be carcinogenic, although data on them are incomplete. These 28 were labeled possible carcinogens.

This project has as its ultimate product an ambient air sampler coupled with an analytical protocol capable of sampling a broad range of chemicals. As such, the evaluation of what is a possible carcinogen has been fairly broad (e.g., one positive established mutagenic test), and chemicals on the resulting list should not be construed as requiring regulation, but only as chemicals in which there are positive mutagenic indicators. In general, however, more data are needed.

SUMMARY REPORT ON THE REVIEW OF THE CARCINOGEN LITERATURE

A summary report has been generated which reviews the available carcinogen literature on more than 125 chemicals. Based on abstracts of the primary literature, and the actual papers where possible, a determination was made in each case as to how the chemical would be classified for this report.

Chemicals for which the overwhelming preponderance of information indicated carcinogenicity or for which regulations had already been enacted to treat the chemical as a carcinogen (e.g., benzene) were classed as probable carcinogens. This generally included positive animal studies coupled with positive mutagenicity tests.

Chemicals on which one or more significant mutagenicity tests were positive (a positive result in at least one well-established mutagen test) with ambiguous carcinogen results were labeled possible carcinogens. It is believed that if enough animal species and routes of administration were tested, these chemicals would most likely be labeled carcinogenic.

The remaining chemicals have been labeled potential carcinogens at some point in the literature. However, a careful review of the presently available literature indicates that they are probable noncarcinogens.

For the 66 probable and possible carcinogens, more data were obtained pertaining to quantity emitted, quantity produced, some market forecasts, persistence in the air (primarily as related to photo-oxidation and reaction with HO and O_3 radicals), and measures of volatility (boiling point and vapor pressure).

A cumulative listing of the summaries of the 125 chemicals evaluated containing the above information along with all of the references to where the information was obtained is included as Appendix A.

PRODUCTION OF POSSIBLE AND PROBABLE CARCINOGENS

In addition to the production figures cited in Appendix A, "A Review of the Carcinogen Literature of 125 Chemicals," production information was gleaned from Chemical and Engineering News, Chemical Marketing Reporter, and from a multiclient research service to which we subscribe. A summary of these additional production volumes is shown in Table 3.

Using data from the above sources, the probable and possible carcinogens were ranked according to production volume, as shown in Tables 4 and 5. The most recent production data were considered most significant.

EMISSION OF POSSIBLE AND PROBABLE CARCINOGENS

Although the ranking of the chemicals in Tables 4 and 5 indicates which materials should be considered "high-volume" chemicals, a more realistic approach to ambient air sampling should depend on the amount of the chemical being released to the atmosphere. Thus the emissions will be the basis for all future ranking of these chemicals. The production figures obtained were utilized to calculate the quantity emitted in cases where literature values for emissions were not available.

The starting point for each of the chemicals was its quantity emitted. Where this information was not available, a simplified assumption was made along the lines of Fuller, et al. [6, PB 264 442], that a fraction (e.g., 0.015) of production is lost to the atmosphere, to determine the quantity emitted per year.

TABLE 3. ADDITIONAL PRODUCTION FIGURES[a]

Chemical	Production, kg	Year	Production, kg	Year
Acrolein	6.1×10^6	1974		
Acrylonitrile	6.8×10^8	1976	5.5×10^8	1975
	6.4×10^8	1974	6.3×10	1973
Aldrin	3.0×10^6	1974		
Allyl chloride[b]	2.1×10^8	1975		
Benzene	6.4×10^8	1976	5.0×10^9	1974
	4.8×10^9	1973		
Benzyl chloride	4.1×10^7	1976	3.2×10^7	1975
	4.1×10^7	1974		
Biphenyl	2.2×10^7	1975		
Captan	4.5×10^6	1975		
Carbon tetrachloride	3.5×10^8	1978	3.7×10^8	1977
	4.9×10^8	1975	4.1×10^8	1975
	4.7×10^8	1974	4.8×10^8	1973
Chlordane	9.6×10^6	1974		
Chloroform	1.5×10^8	1976	1.3×10^8	1975
Chloroprene[c]	1.4×10^8	1976		
Dichlorobutene[d]	1.4×10^8	1976		
Dichloropropene[e]	2.5×10^7	1976		
Dichlorovinyl dimethyl phosphate	3.2×10^6	1976		
Di-(2-ethylhexyl) phthalate	1.8×10^8	1974		
Dinitrotoluene[f]	1.0×10^8	1976		
Epichlorohydrin	8.2×10^7	1973		
Ethylene dibromide	1.5×10^8	1973		
Ethylene dichloride	5.5×10^9	1977	5.5×10^9	1976
	4.5×10^9	1974	3.5×10^9	1974
	4.2×10^9	1973		
Ethylene oxide	2.0×10^9	1975	1.7×10^9	1975
	1.9×10^9	1974	1.9×10^9	1973
Formaldehyde	2.9×10^9	1978	2.8×10^9	1977
	2.5×10^9	1976	2.7×10^9	1974
	2.9×10^9	1973		
Heptachlor	9.1×10^5	1974		
Hexachlorobenzene	4.5×10^5	1974		
Mercaptobenzothiazole	2.8×10^6	1974		
Methyl chloride	$1.x \times 10^8$	1976	1.4×10^8	1975
Methylenediamine[g]	1.6×10^8	(1976)		
Morpholine	1.1×10^7	1974	1.1×10^7	1973
1-Naphthylamine	decreasing			
Nitrochlorobenzene[h]	6.2×10^7	1976	4.9×10^7	1974
	4.7×10^7	1973		
Pentachlorophenol	1.8×10^7	1975	2.3×10^7	1974
	2.2×10^7	1973		
Propylene oxide	7.7×10^8	1976	6.8×10^8	1975
	7.3×10^8	1975	7.9×10^8	1974
Styrene	3.0×10^9	1977	2.9×10^9	1976
	2.1×10^9	1975	2.7×10^9	1974
	2.7×10^9	1973		
Tetrachloroethylene	3.3×10^8	1976	3.2×10^8	1975
	3.3×10^8	1974	3.2×10^8	1973
Tetraethyl lead	1.6×10^8	1973		
Tetraethyl lead and tetramethyl lead	3.0×10^8	1976	3.1×10^8	1975
Toluene-2,4-diamine	1.0×10^8	1976		
Trichloroethylene	1.6×10^8	1975	2.0×10^8	1974
Trichlorophenol[i]				

(continued)

TABLE 3 (continued)

Chemical	Production, kg	Year	Production, kg	Year
Vinyl acetate	4.8×10^8	1975	6.4×10^8	1974
	1.0×10^8	1974	6.8×10^8	1973
Vinyl bromide[j]	1.9×10^5	1975		
Vinyl chloride	2.6×10^9	1976	1.8×10^9	1975
	2.5×10^9	1974	2.4×10^9	1973
Vinylidene chloride	7.0×10^7	1976		
Chrysene[k]	1.7×10^4	1977		

[a] Production figures cited are derived from the following sources, with no more than two years of figures per reference: Chemical and Engineering News, June, 1975; Chemical Marketing Reporter, various issues; and a multiclient research service subscription (complete information is not available to the general public).

[b] Capacity.

[c] The 1976 production of polychloroprene was 1.4×10^8 kg. Assume 1.4×10^8 kg of chloroprene was produced for this use.

[d] Butadiene is converted to either 2,3-dichlorobutene-1 for chloroprene manufacture of 1,4-dichlorobutene-2 for adiponitrile manufacture. In 1976, 1.4×10^8 kg polychloroprene was produced. Assume 1.4×10^8 dichlorobutene may have been used.

[e] The Dow capacity for dichloropropene was 14 million kilograms in 1976 while the Shell capacity for a dichloropropene/dichloropropane mixture was 22 million kilograms. Assume half the Shell mixture was dichloropropene and the capacity equals the production to give 2.5×10^8 kg for both facilities.

[f] Dinitrotoluene is an intermediate in the manufacture of toluene diamine. A gross assumption would be to equate the production of these chemicals.

[g] 6.6×10^8 kg formaldehyde was used to make methylenedianiline, with 0.41 kg formaldehyde used for each kg of methylenedianiline produced. This yields a production of 1.6×10^8 kg methylenedianiline.

[h] In 1976, 2.4×10^7 kg of HNO_3 were used to make nitrochlorobenzene where 0.42 kg HNO_3 is used to make 1.0 kg nitrochlorobenzene. Therefore, the 1976 production of nitrochlorobenzene was about 6.2×10^7 kg.

[i] The use of 2,4,5-T herbicide has been restricted by the government.

[j] To produce SEF® modacrylic, 9% vinyl bromide is used. Assume 25% of the 1.14×10^7 kg modacrylic capacity was SEF and it was operating at 68% capacity to give a vinyl bromide consumption of 1.9×10^5 kg.

[k] Assume 150 mg chrysene per gram organic atomospheric particulate matter. MRC Source Assessment Data Base, July 1977, cites 1.13×10^8 kg of benzene soluble organic particulate matter emitted from stationary sources. This reduces to 1.7×10^4 kg chrysene emitted (and produced).

TABLE 4. PRODUCTION-RANKED PROBABLE CARCINOGENS

Rank	Chemical	Production, kg	Year
1	Ethylene dichloride	5.5×10^{9}	1977
2	Vinyl chloride	2.6×10^{9}	1976
3	Acrylonitrile	6.8×10^{8}	1976
4	Benzene	6.4×10^{8}	1976
5	Carbon tetrachloride	3.8×10^{8}	1977
6	Tetrachloroethylene	3.2×10^{8}	1976
7	Chloroform	1.5×10^{8}	1976
8	Trichloroethylene	1.4×10^{8}	1976
9	Dichlorobutene	1.4×10^{8}	1976
10	Epichlorohydrin	1.4×10^{8}	1973[a]
11	Ethylene dibromide	1.2×10^{8}	1975
12	Toluenediamine	1.0×10^{8}	1976
13	Dinitrotoluene	1.0×10^{8}	1976[b]
14	Vinylidene chloride	7.0×10^{7}	1976
15	Benyl chloride	4.1×10^{7}	1976
16	DDT	2.0×10^{7}	1971
17	Hydrazine	1.7×10^{7}	1974
18	Chlordane	9.6×10^{6}	1974
19	Dioxane	7.4×10^{6}	1973
20	Benzidene	4.7×10^{6}	1976[c]
21	Captan	4.5×10^{6}	1975
22	Methylene bis(chloroaniline)	3.5×10^{6}	1972
23	Ethylenimine	2.2×10^{6}	1974
24	Dichlorobenzidine	2.1×10^{6}	1976[c]
25	Heptachlor	9.1×10^{5}	1974
26	Chlorobenzilate	9.0×10^{5}	1976[c]
27	Benzo(a)pyrene	8.3×10^{5}	1977[c,d]
28	Dimethylhydrazine	$<5.0 \times 10^{5}$	1973
29	Chrysene	1.7×10^{4}	1977[d]
30	Diaminanisole	1.4×10^{4}	1978[c,e]
31	Benz(a)anthracene	1.0×10^{4}	1977[c,f]
32	Tetrachloroethane	9.4×10^{3}	1977[c,d]
33	Bis(chloromethyl) ether	$<4.5 \times 10^{2}$	1974
34	Nitrosodimethylamine	$<4.5 \times 10^{2}$	1977[c]
35	Ethyl carbamate (urethane)	$<4.5 \times 10^{2}$	1974[c]
36	Trichlorofon	1.0×10^{2}	1977[c,d]
37	Polychlorinated biphenyls (1.8×10^{7})	-0-	1974[g]
38	Aldrin (3.0×10^{6})	-0-	1974[g]

[a] Average of several different numbers.

[b] Intermediate in toluene diamine manufacture. Assumed equal production.

[c] Document published in cited year which contains production figure.

[d] Assume emitted quantity equals produced quantity.

[e] Quantity imported.

[f] Assume emission is 1% of production from stationary sources and ignore nonstationary sources.

[g] Current production assumed to be zero, but literature values also cited.

TABLE 5. PRODUCTION-RANKED POSSIBLE CARCINOGENS

Rank	Chemical	Production, kg	Year
1	Styrene	3.0×10^9	1977
2	Formaldehyde	2.1×10^9	1975
3	Ethylene oxide	2.0×10^9	1975
4	Cumene hydroperoxide	1.4×10^9	1974
5	Propylene oxide	7.7×10^8	1976
6	Vinyl acetate	4.8×10^8	1975
7	Allyl chloride	2.1×10^8	1975
8	Di-(2-ethylhexyl) phthalate	1.8×10^8	1974
9	Methyl chloride	1.7×10^8	1976
10	Tetraethyl lead	1.6×10^8	1973
11	Chloroprene	1.6×10^8	1974
12	Nitrochlorobenzene	4.9×10^7	1974
13	Pentachlorophenol	2.1×10^7	1975[a]
14	Dichloropropene	2.8×10^7	1976
15	Acrolein	1.4×10^7	1974[a]
16	Methylenedianiline	1.3×10^7	72, 76[a]
17	Morpholine	1.1×10^7	1974
18	Hexachlorobutadiene	8.0×10^6	1975[b]
19	Dichlorovinyl dimethyl phosphate	3.2×10^6	1976
20	1-Naphthylamine	3.2×10^6	1974
21	Mercaptobenzothiazole	2.8×10^6	1974
22	1,1-Dichloroethane	2.6×10^6	1977[b,c]
23	Di-tert-butyl peroxide	1.4×10^6	1977[b]
24	Hexachlorobenzene	4.5×10^5	1974
25	Vinyl bromide	1.9×10^5	1975[d]
26	Dichloronaphthoquinone	9.0×10^2	1977[b,c]
27	Trichlorophenol	5.0×10^2	1977[b,c]
28	Biphenyl (2.2×10^7)	-0-	1975[e]

[a] Average of production figures.

[b] Date of publication of reference.

[c] Assume emissions are equal to production.

[d] Rough estimate.

[e] Current production is assumed to be zero since the production of polychlorinated biphenyls (PCB's) has stopped. Literature value is given for comparison.

In cases where this type of calculation was needed, the nature of the chemical involved was considered. A fraction such as 0.01 was assumed for chemicals which are used as intermediates for other chemicals or in other nondispersive manners, while the fraction 1.00 was used when it was assumed that all of the chemical produced is deliberately released to the environment. (In one case, 1.03 was used; it represents 100% of production plus a 3% fugitive emission from production sources.) Much more weight has been placed on figures from the literature which have been more extensively evaluated than on those numbers where an emission factor had been used to calculate emissions. Where no other values were available, emissions were assumed to be a fraction of production as related above. The emissions-ranked probable and possible carcinogens are shown in Tables 6 and 7.

Where more than one significant emission figure was available, the log average was used, with the MRC Source Assessment Data Base emissions given twice the weight of other information.

ATMOSPHERIC PERSISTENCE OF POSSIBLE AND PROBABLE CARCINOGENS

In this project, atmospheric carcinogens are of interest as opposed to occupational carcinogens. For carcinogens to be present in the atmosphere, they need to have some stability. A few of the carcinogens are rapidly degraded by light, moisture, or other factors as opposed to a few other that are known to have a very long environmental persistence. It seems reasonable that carcinogenic chemicals that degrade in moments in the atmosphere should be considered less significant than those that are very persistent in the environment.

Several time frames were considered to determine how environmental persistence should be regarded as a factor in the concentration of carcinogens in the atmosphere. A long time frame (e.g., 30 days) would allow for the disappearance of those materials that degrade as they move away from the source. However, many of the sources of emissions are located near cities in which the population would be exposed in a matter of a few hours. Twenty-four hours was chosen as a reasonable time.

The literature references used for this calculation are shown in Appendix I in the summaries of each of the chemicals. The half-life used was that quoted for photodegradation, HO radical, and O_3 radical reactions with the test chemicals. Tables 8 and 9 show the annual quantities of probable and possible carcinogens emitted that would be in the atmosphere 24 hours after emission.

If no data were available on degradation, it was assumed that the quantity emitted remained after 24 hours. In general, this persistence correction factor was only significant for the few chemicals indicated in the literature to have atmospheric half-lives of minutes to hours.

TABLE 6. EMISSIONS-RANKED PROBABLE CARCINOGENS[a]

Rank	Chemical	Emissions, kg/yr
1	Trichloroethylene	1.7×10^{8}
2	Tetrachloroethylene	1.2×10^{8}
3	Vinyl chloride	1.2×10^{8}
4	Ethylene dichloride	9.8×10^{7}
5	Benzene	7.4×10^{7}
6	Chlordane[b]	9.6×10^{6}
7	Dioxane[b]	7.4×10^{6}
8	Ethylene dibromide	4.8×10^{6}
9	Chloroform	2.6×10^{6}
10	Carbon tetrachloride	1.6×10^{7}
11	Chlorobenzilate[b]	9.0×10^{5}
12	Dichlorobutene	8.7×10^{5}
13	Benzo(a)pyrene[b]	8.3×10^{5}
14	Toluene-2,4-diamine	4.4×10^{5}
15	Vinylidene chloride	4.1×10^{5}
16	Benzyl chloride[c]	4.1×10^{5}
17	Acrylonitrile	3.7×10^{5}
18	Epichlorohydrin	2.2×10^{5}
19	Benzidine	7.0×10^{4}
20	Methylene bis(chloroaniline)	4.5×10^{4}
21	Ethylenimine	2.7×10^{4}
22	DDT[d]	1.9×10^{4}
23	Chrysene	1.7×10^{4}
24	Heptachlor	1.1×10^{4}
25	Tetrachloroethane[b]	9.4×10^{3}
26	Dimethylhydrazine[c]	$<5.0 \times 10^{3}$
27	Dichlorobenzidine	4.5×10^{3}
28	Hydrazine	3.5×10^{3}
29	Dinitrotoluene	4.0×10^{2}
30	Diaminoanisole[c]	1.4×10^{2}
31	Trichlorfon	1.0×10^{2}
32	Benz(a)anthracene[c]	$<1.0 \times 10^{2}$
33	Bis(chloromethyl) ether	$<1.0 \times 10^{2}$
34	Captan	$<1.0 \times 10^{2}$
35	Nitrosodimethylamine	$<1.0 \times 10^{2}$
36	Ethyl carbamate (urethane)[c]	4.5
37	Aldrin (3.0×10^{6})[b,e]	0
38	Polychlorinated biphenyls (1.8×10^{5})[c,e]	0

---

[a] When more than one significant emission figure is available, the log average is used, with the MRC data base figure given twice the weight of the other values.

[b] Assumed emission factor of 1.00 of production.

[c] Assumed emission factor of 0.01 of production.

[d] Emitted from stationary sources (MRC Source Assessment Data Base, July 1977).

[e] Current production (emission) of zero, but average literature values also given.

TABLE 7. EMISSIONS-RANKED POSSIBLE CARCINOGENS[a]

Rank	Chemical	Emissions, kg/yr
1	Formaldehyde	4.8×10^7
2	Dichloropropene[b]	2.8×10^7
3	Pentachlorophenol[b]	2.1×10^7
4	Cumene hydroperoxide	2.1×10^7
5	Methyl chloride	1.6×10^7
6	Ethylene oxide	9.7×10^6
7	Hexachlorobutadine	7.3×10^6
8	Chloroprene	6.9×10^6
9	Tetraethyl lead	6.6×10^6
10	Acrolein	6.5×10^6
11	Styrene	5.6×10^6
12	Morpholine	5.5×10^6
13	Propylene oxide	4.4×10^6
14	1,1-Dichloroethane	2.6×10^6
15	Di-(2-ethylhexyl) phthalate	2.4×10^6
16	Allyl chloride	7.1×10^5
17	Vinyl acetate	6.8×10^5
18	Hexachlorobenzene	2.3×10^5
19	1-Naphthylamine[c]	3.2×10^4
20	Mercaptobenzothiazole	2.7×10^4
21	Methylenedianiline	2.6×10^4
22	Di-tert-butyl peroxide[c]	1.4×10^4
23	Vinyl bromide	4.0×10^3
24	Dichloronaphthoquinone	9.0×10^2
25	Trichlorophenol	5.0×10^2
26	Nitrochlorobenzene	3.0×10^2
27	Dichlorovinyl dimethyl phosphate	2.0×10^2
28	Biphenyl (9.2×10^4)[d]	0

[a] When more than one significant emission figure is available, the log average is used, with the MRC data base figure given twice the weight of the other values.

[b] Assumed a release factor of 1.00 of production.

[c] Assumed a release factor of 0.01 of production.

[d] Current production of PCB's is zero, so assumed biphenyl emissions also zero. Literature value is also given.

TABLE 8. EMISSIONS/PERSISTENT-RANKED PROBABLE CARCINOGENS

Rank	Chemical	Atmospheric half-life	Emissions, kg/yr, remaining after 24 hours
1	Ethylene dichloride	234 h	9.1×10^{7}
2	Tetrachloroethylene	2.0 d	8.5×10^{7}
3	Benzene	3.0 d	5.9×10^{7}
4	Vinyl chloride	12 h	3.0×10^{7}
5	Trichloroethylene	0.3 d	1.7×10^{7}
6	Carbon Tetrachloride	10 wk	1.6×10^{6}
7	Chlordane	N.A.[a]	9.6×10^{6}
8	Ethylene dibromide	20 h	2.1×10^{6}
9	Dioxane	9.6 h	1.3×10^{6}
10	Dichlorobutene	N.A.	8.7×10^{5}
11	Benzo(a)pyrene	N.A.	8.3×10^{5}
12	Chlorobenzilate	N.A.	9.0×10^{5}
13	Chloroform	13 h	7.2×10^{5}
14	Toluene-2,4-dimaine	N.A.	4.4×10^{5}
15	Benzyl chloride	N.A.	4.1×10^{5}
16	Acrylonitrile	N.A.	3.7×10^{5}
17	Vinylidene chloride	24 h	2.1×10^{5}
18	Benzidine	1 d	3.5×10^{4}
19	DDT	N.A.	1.9×10^{4}
20	Ethylenimine	1.5 d	1.7×10^{4}
21	Chrysene	-	1.7×10^{4}
22	Methylene bis(chloroaniline)	12 h	1.1×10^{4}
23	Heptachlor	N.A.	1.1×10^{4}
24	Tetrachloroethane	N.A.	9.4×10^{3}
25	Dichlorobenzidine	1 d	2.3×10^{3}
26	Epichlorohydrin	3 h	8.6×10^{2}
27	Dinitrotoluene	N.A.	4.0×10^{2}
28	Diaminoanisole	N.A.	1.4×10^{2}
29	Trichlorofon	N.A.	1.0×10^{2}
30	Captan	N.A.	$<1.0 \times 10^{2}$
31	Benz(a)anthracene	N.A.	$<1.0 \times 10^{2}$
32	Ethyl carbamate (urethane)	N.A.	4.5
33	Dimethylhydrazine	2.1 h	2.0
34	Hydrazine	1 h	>1.0
35	Nitrosodimethylamine	1 h	>1.0
36	Bis(chloromethyl) ether	25 min	>1.0
37	Aldrin (3.0×10^{6})[b]	N.A.	0
38	Polychlorinated biphenyls (1.7×10^{5})[c]	N.A.	0

---

[a] Persistence data could not be found. Assumed that the chemical does not degrade appreciably in 24 hours.

[b] Current production assumed to be zero, but literature value also cited.

[c] Primary source of biphenyl emissions was production of polychlorinated biphenyls, which has been stopped. Average literature value given in parentheses.

TABLE 9. EMISSIONS/PERSISTENCE-RANKED POSSIBLE CARCINOGENS

Rank	Chemical	Atmospheric half-life	Emissions, kg/yr, remaining after 24 hours
1	Dichloropropene	3 d	2.2×10^7
2	Pentachlorophenol	N.A.[a]	2.1×10^7
3	Methyl chloride	1 yr	1.6×10^7
4	Styrene	N.A.	5.6×10^6
5	Morpholine	N.A.	5.5×10^6
6	Tetraethyl lead	2 d	4.7×10^6
7	Hexachlorobutadiene	<1 d	3.4×10^6
8	1,1-Dichloroethane	N.A.	2.6×10^6
9	Chloroprene	<10 h	1.3×10^6
10	Di-(2-ethylhexyl) phthalate	1 d	1.2×10^6
11	Vinyl acetate	N.A.	6.8×10^5
12	Hexachlorobenzene	2 d	1.6×10^5
13	Allyl chloride	9 h	1.1×10^5
14	Cumene hydroperoxide	3 h	8.2×10^4
15	Ethylene oxide	3 h	3.8×10^4
16	Methylenedianiline	N.A.	2.6×10^4
17	Propylene oxide	3 h	1.7×10^4
18	Acrolein	2.6 h	1.1×10^4
19	Di-tert-Butyl peroxide	79 h	1.1×10^4
20	1-Naphthylamine	12 h	8.0×10^3
21	Mercaptobenzothiazole	9.6 h	4.8×10^3
22	Vinyl bromide	N.A.	4.0×10^3
23	Dichloronaphthoquinone	N.A.	9.0×10^2
24	Trichlorophenol	N.A.	5.0×10^2
25	Nitrochlorobenzene	N.A.	3.0×10^2
26	Dichlorovinyl dimethyl phosphate	N.A.	2.0×10^2
27	Formaldehyde	1.2 h	45.8
28	Biphenyl (9.2×10^4)[b]	N.A.	0

---

[a] N.A. - Persistence data could not be found. Assumed that the chemical does not degrade appreciably in 24 hours.

[b] Primary source of biphenyl emissions was production of polychlorinated biphenyls, which has been stopped. Average literature value given in parentheses.

POTENCY OF POSSIBLE AND PROBABLE CARCINOGENS

It was decided that the potency of the possible and probable carcinogens would be determined, where possible, by the average of the mutagenic potency relative to benzo(a)pyrene using two different mutagenic tests and the carcinogenic potency relative to benzo(a)pyrene using two different species or routes of administration.

Data required for potency calculations based on any specific test system was unavailable for many compounds. This is particularly true for carcinogenic data; such information is often conflicting when it can be found. It is important, however, to take into account the fact that some chemicals are more potent carcinogens than others. Absolute potency data, however, should not be required in order to determine the relative significance of a number of chemicals. Thus, a system to determine relative potencies was devised. Several decisions were made concerning how the data would be treated:

(1) Both mutagenic and carcinogenic potencies would be used, with the final result being an average of the two numbers.

(2) Missing data would be handled by using an average potency determined from the rest of the compounds within each group (possible vs. probable).

(3) Benzo(a)pyrene was selected as the basis for comparisons because of the large number of test systems in which it has been evaluated.

(4) The relative carcinogenic potencies would be determined by comparing only data from the same species and route of administration. For example, if chlordane had been evaluated in hamsters by addition of the chemical to their food, only benzo(a)pyrene data generated by the oral route on hamsters would be used to determine the relative potency of these two compounds.

(5) When several sets of test data were available, the log average of the relative carcinogenic (or mutagenic) potencies would be used to assure that results from any one test would not overshadow other results which were orders of magnitude different.

(6) Average mutagenic potencies would be assigned to test compounds even if they were found to be negative by the test concerned. For example, a logarithmic average of the Ames test data from all of the compounds on both carcinogen lists (possible and probable) has been found to be 8.3×10^{-3} revertants per nanomole. In our computations, this average mutagenic potency was arbitrarily assigned to all chemicals

that have been found positive on the Ames test with no data reported, or have been found negative on the Ames test. This only assumes that unless other data are known, the chemical has an average potency. For the viral enhancement data, the average potency of 4.1×10^{-3} µg/ml was assigned to chemicals for which there were no data. The average of these two numbers gives a relative mutagenic potenty of 5.3×10^{-3} for any chemicals that have no mutagenic data cited in the literature. Likewise, the average relative carcinogenic potency was found to be 1.4×10^{-2}.

(7) In test systems where no benzo(a)pyrene data were available, secondary standards would be used to back calculate a potency relative to benzo(a)pyrene.

RELATIVE MUTAGENIC POTENCY

Efforts were made to assemble mutagenic potency data. In addition to the data cited in Appendix A, some data are displayed in Tables 10, 11, and 12.

TABLE 10. RELATIVE MUTAGENIC POTENCY
[Compared to benzo(a)pyrene]

Chemical	Potency *S. typhimurium*, rev/nmole	Relative potency
Allyl chloride [9]	61	5.0×10^{-1}
DDT [10]	0.01	8.5×10^{-5}
Diaminoanisole [11]	5.66	4.7×10^{-2}
Dichlorovinyl dimethyl phosphate [12]	1.35	1.1×10^{-2}
Hydrazine [13]	0.043	3.6×10^{-4}
Methyl chloride [14]	0.12	9.9×10^{-4}
Tetrachloroethane [15]	0.008	6.4×10^{-5}
Toluene-2,4-diamine [16]	0.43	3.6×10^{-2}

---

[9] Mutation Research, 57:11-15, 1978.

[10] Journal of Agricultural and Food Chemistry, 24:560, 1976.

[11] Biochemical Pharmacology, 26(8):729-734, 1977.

[12] Mutation Research, 31:268-269, 1975.

[13] Mutation Research, 40(2):73-83, 1976.

[14] Mutation Research, 40(3):273-275, 1976.

[15] Cancer Research, 34:2576, 1974.

[16] Proceedings of the National Academy of Sciences of the United States, 72(6):2423-2427, 1975.

TABLE 11. PRELIMINARY MUTAGENIC POTENCY DATA

Chemical	*S. typhimurium*, rev/mole	Viral enhancement, µg/ml
Acrylonitrile	1.2×10^{-2}	8.0×10^{-4}
Benz(a)anthracene	9.0×10^{-2}	1.6×10^{-2}
Benzidine	1.2×10^{-2}	1.6×10^{-4}
Benzo(a)pyrene	1	1
Benzyl chloride	1.7×10^{-4}	
Captan	2.1×10^{-1}	
Chlordane		1.6×10^{-2}
Chrysene	3.1×10^{-1}	
Dichlorobenzidine		6.4×10^{-3}
Dichlorobutene	2.4×10^{-2}	
Dimethylhydrazine		3.2×10^{-3}
Ethylene dibromide	5.0×10^{-4}	1.6×10^{-4}
Ethylene dichloride		1.6×10^{-4}
Ethylenimine	1.7×10^{-2}	
Heptachlor		8.0×10^{-3}
Hydrazine		8.0×10^{-5}
4,4-Methylene bis(2-chloroaniline)	2.2×10^{-2}	3.2×10^{-2}
Nitrosodimethylamine	1.7×10^{-4}	Negative
Vinyl chloride	2.9×10^{-4}	Positive
Vinylidene chloride	7.3×10^{-4}	
Chloroprene	2.5×10^{-3}	6.4×10^{-4}
Formaldehyde		1.3×10^{-1}
1-Naphthylamine	3.5×10^{-3}	8.0×10^{-4}
Pentachlorophenol		8.0×10^{-4}
Propylene oxide		3.2×10^{-4}
Tetraethyl lead		6.4×10^{-3}
Vinyl acetate		1.3×10^{-3}
Vinyl bromide	1.3×10^{-3}	

TABLE 12. OTHER MUTAGEN DATA TO CONSIDER

Drosophila melanogaster [17]	
Nitrosodimethylamine	- recessive lethal mutations at 6.8 nmole
Dimethylhydrazine	- recessive lethal mutations at 2.0 nmole
DDT	- recessive lethal mutations at 0.14 nmole
Ethylene dibromide	- recessive lethal mutations at 0.3 nmole
Vinyl chloride	- causes recessive lethal mutations
Saccharomyces cerevisiae [18]	
Dichlorovinyl dimethyl phosphate	- 19 mole for 6 h gives 11.7 ade^2 and 29 trp^5 mutants
Pentachlorophenol	- 0.19 mole for 6 h gives 6.6 ade^2 and 4.3 trp^5 mutants
Ethylene dibromide	- 0.17 mole for 27 h gives 10.8 ade^2 and 8.8 trp^5 mutants
Captan	- 0.17 mole for 27 h gives 12.5 ade^2 and 17.7 trp^5 mutants

---

[17] International Agency for Research on Cancer Scientific Publication No. 12, 1976. pp. 61, 125, and 623.

[18] International Agency for Research on Cencer Scientific Publication No. 10, 1974. pp. 161-181.

RELATIVE CARCINOGENIC POTENCY

A major problem encountered is that differing routes of administration may cause the potency relative to benzo(a)pyrene to vary by as much as 10^6. For example, benzene on mouse skin has a toxic dose low (TDLo) of 1,200 g/kg (over a 49-week period), while benzo(a)pyrene has a TDLo of 2 μg/kg for a relative potency of 2×10^{-9}. Subcutaneously, 1 mg/kg benzene has been suggested to cause cancer (no controls) versus 0.004 mg benzo(a)pyrene for a relative potency of 4×10^{-3} and a difference in potency of six orders of magnitude. In spite of the problems associated with this type of calculation, an average mutagenic potency and an average carcinogenic potency was calculated for each chemical, as shown in Tables 13 and 14. The log average of these two numbers was then determined as also shown in Tables 13 and 14.

PRIORITIZATION OF POSSIBLE AND PROBABLE CARCINOGENS

Since this project is directed at atmospheric carcinogens, some consideration should be given to whether a specific chemical is much more likely to be found in the air, in water, or in the soil or other solids. Many different parameters could be used to put more emphasis on chemicals which are atmospheric pollutants such as whether the chemicals at ambient temperature are solids, liquid, or a gas. The solid-liquid-gas classification would not distinguish between highly volatile liquids such as chloroform and benzene and liquids with very low vapor pressures such as the polychlorinated biphenyls. Since boiling point data are readily available and correlate well with vapor pressure, it was thought that boiling point might be a valid parameter to consider. On the other hand, solids might be in the atmosphere as particulate matter or carried on other particulates. Thus it was decided not to include these data in the prioritization model. Many data on various properties of the selected possible and probable carcinogens, however, are listed in Appendix A for each chemical.

The prioritization model that was used to determine which significant carcinogens in the atmosphere should be sampled for this project results in an equivalent kilograms of benzo(a)pyrene emitted per year after 24 hours in the atmosphere. This number is generated by multiplying: (a) the kilograms emitted per year, times (b) the fraction present after 24 hours, times (c) the potency relative to benzo(a)pyrene.

From the top chemicals in these prioritizations, 20 chemicals were selected which represent a variety of chemical types. Of these 20 chemicals, 15 will be selected by EPA for use in the latter portions of this contract and contract 68-02-2774 (portable carcinogen tester) as key chemicals in the analysis of ambient air. These are footnoted on Tables 15 and 16, which rank the probable and possible carcinogens by equivalent emissions of benzo(a)pyrene after 24 hours.

TABLE 13. RELATIVE MUTAGENIC/CARCINOGENIC POTENCY OF PROBABLE CARCINOGENS
[Compared to benzo(a)pyrene]

	Chemical	Mutagenicity compared to B(a)P	Carcinogenicity compared to B(a)P	Average mutagenic/ carcinogenic potency
1	Benzo(a)pyrene	1.0	1.0	1.0
2	DDT	$-(5.8 \times 10^{-3})$[a,b]	3.7	1.5×10^{-1}
3	Heptachlor	8.1×10^{-3}	1.8	1.2×10^{-1}
4	Nitrosodimethylamine	8.3×10^{-4}	11.0	9.6×10^{-2}
5	Aldrin	(5.8×10^{-3})	5.0×10^{-1}	5.4×10^{-2}
6	Benz(a)anthracene	3.8×10^{-2}	3.0×10^{-2}	3.4×10^{-2}
7	Polychlorinated biphenyls	(5.8×10^{-3})	8.0×10^{-2}	2.2×10^{-2}
8	Bis(chloromethyl) ether	$+(5.8 \times 10^{-3})$[c]	7.0×10^{-2}	2.0×10^{-2}
9	Ethylenimine	8.3×10^{-3}	4.6×10^{-2}	2.0×10^{-2}
10	Chloroform	(5.8×10^{-3})	5.0×10^{-2}	1.7×10^{-2}
11	Diaminoanisole	1.4×10^{-2}	$+(1.4 \times 10^{-2})$	1.4×10^{-2}
12	Trichlorfon	(5.8×10^{-3})	2.8×10^{-2}	1.3×10^{-2}
13	Carbon tetrachloride	$-(5.5 \times 10^{-3})$	2.5×10^{-2}	1.2×10^{-2}
14	Dichlorobenzidine	1.1×10^{-1}	8.1×10^{-4}	9.4×10^{-3}
15	Ethylene dibromide	2.8×10^{-4}	0.31	9.3×10^{-3}
16	Dinitrotoluene	(5.8×10^{-3})	$+(1.4 \times 10^{-2})$	9.0×10^{-3}
17	Tetrachloroethylene	(5.8×10^{-3})	$+(1.4 \times 10^{-2})$	9.0×10^{-3}
18	Captan	5.6×10^{-2}	7.8×10^{-4}	6.6×10^{-3}
19	Toluene-2,4-diamine	1.2×10^{-2}	2.9×10^{-3}	6.0×10^{-3}
20	Vinylidene chloride	1.7×10^{-3}	$+(1.4 \times 10^{-2})$	4.9×10^{-3}
21	Benzene	(5.8×10^{-3})	4.0×10^{-3}	4.8×10^{-3}
22	Dichlorobutene	9.9×10^{-3}	2.3×10^{-3}	4.8×10^{-3}
23	Acrylonitrile	4.5×10^{-4}	5.0×10^{-2}	4.7×10^{-3}
24	Trichloroethylene	6.0×10^{-3}	3.1×10^{-3}	4.3×10^{-3}
25	Methylene bis(chloroaniline)	2.7×10^{-2}	7.0×10^{-4}	4.3×10^{-3}
26	Ethylene dichloride	1.2×10^{-3}	$+(1.4 \times 10^{-2})$	4.1×10^{-3}
27	Chlordane	1.2×10^{-2}	8.7×10^{-4}	3.2×10^{-3}
28	Ethyl carbamate (urethane)	$-(5.8 \times 10^{-3})$	1.8×10^{-3}	3.2×10^{-3}
29	Chrysene	3.6×10^{-2}	2.5×10^{-2}	3.0×10^{-3}
30	Vinyl chloride	2.5×10^{-3}	3.0×10^{-3}	2.7×10^{-3}
31	Tetrachloroethane	3.1×10^{-4}	$+(1.4 \times 10^{-2})$	2.1×10^{-3}
32	Dioxane	(5.8×10^{-3})	6.2×10^{-4}	1.9×10^{-3}
33	Chlorobenzilate	(5.8×10^{-3})	6.0×10^{-4}	1.9×10^{-3}
34	Epichlorohydrin	$+(5.8 \times 10^{-3})$	4.0×10^{-4}	1.5×10^{-3}
35	Dimethylhydrazine	5.2×10^{-3}	4.6×10^{-4}	1.5×10^{-3}
36	Hydrazine	1.7×10^{-4}	1.2×10^{-2}	1.4×10^{-3}
37	Benzidine	1.4×10^{-3}	6.5×10^{-4}	9.5×10^{-4}
38	Benzyl chloride	8.3×10^{-4}	1.3×10^{-4}	3.3×10^{-4}

[a] Parentheses indicate that no statistical data were available, so an average potency was used.

[b] A minus indicates that the chemical was not a mutagen by the test reported.

[c] A plus indicates that the chemical was positive on the test, but no numerial data were reported.

TABLE 14. RELATIVE MUTAGENIC/CARCINOGENIC POTENCY OF POSSIBLE CARCINOGENS
[Compared to benzo(a)pyrene]

	Chemical	Mutagenicity compared to B(a)P	Carcinogenicity compared to B(a)P	Average mutagenic/ carcinogenic potency
1	Hexachlorobenzene	(5.8 x 10^{-3})[a]	5.9 x 10^{-1}	5.8 x 10^{-2}
2	Formaldehyde	3.3 x 10^{-2}	5.9 x 10^{-3}	1.4 x 10^{-2}
3	Tetraethyl lead	7.3 x 10^{-3}	1.7 x 10^{-2}	1.1 x 10^{-2}
4	Dichlorohaphthoquinone	(5.8 x 10^{-3})	1.7 x 10^{-2}	9.9 x 10^{-3}
5	Allyl chloride	4.5 x 10^{-2}	-(1.9 x 10^{-3})[b]	9.3 x 10^{-3}
6	Chloroprene	1.3 x 10^{-3}	6.4 x 10^{-2}	9.1 x 10^{-3}
7	Mercaptobenzothiazole	(5.8 x 10^{-3})	5.2 x 10^{-3}	5.5 x 10^{-3}
8	Hexachlorobutadiene	(5.8 x 10^{-3})	3.9 x 10^{-3}	4.8 x 10^{-3}
9	Dichlorovinyl dimethyl phosphate	1.1 x 10^{-2}	-(1.9 x 10^{-3})	4.6 x 10^{-3}
10	Pentachlorophenol	2.6 x 10^{-3}	7.6 x 10^{-3}	4.0 x 10^{-3}
11	Nitrochlorobenzene	(5.8 x 10^{-3})	-(1.9 x 10^{-3})	3.3 x 10^{-3}
12	Styrene	+(5.8 x 10^{-3})[c]	-(1.9 x 10^{-3})	3.3 x 10^{-3}
13	Acrolein	+(5.8 x 10^{-3})	-(1.9 x 10^{-3})	3.3 x 10^{-3}
14	Ethylene oxide	(5.8 x 10^{-3})	+(1.9 x 10^{-3})	3.3 x 10^{-3}
15	1,1-Dichloroethane	+(5.8 x 10^{-3})	-(1.9 x 10^{-3})	3.3 x 10^{-3}
16	Dichloropropene	(5.8 x 10^{-3})	-(1.9 x 10^{-3})	3.3 x 10^{-3}
17	Di-(2-ethylhexyl) phthalate	(5.8 x 10^{-3})	1.3 x 10^{-3}	2.7 x 10^{-3}
18	Vinyl acetate	3.3 x 10^{-3}	-(1.9 x 10^{-3})	2.5 x 10^{-3}
19	Methylenedianiline	+(5.8 x 10^{-3})	1.1 x 10^{-3}	2.5 x 10^{-3}
20	Vinyl bromide	2.3 x 10^{-3}	-(1.9 x 10^{-3})	2.1 x 10^{-3}
21	Morpholine	(5.8 x 10^{-3})	7.3 x 10^{-4}	2.1 x 10^{-3}
22	Methyl chloride	2.0 x 10^{-3}	-(1.9 x 10^{-3})	2.0 x 10^{-3}
23	Di-tert-butyl peroxide	(5.8 x 10^{-3})	6.0 x 10^{-4}	1.9 x 10^{-3}
24	1-Naphthylamine	1.7 x 10^{-3}	1.7 x 10^{-3}	1.7 x 10^{-3}
25	Propylene oxide	1.6 x 10^{-3}	1.4 x 10^{-4}	4.7 x 10^{-4}
26	Trichlorophenol	(5.8 x 10^{-3})	6.1 x 10^{-5}	5.9 x 10^{-4}
27	Cumene hydroproxide	-(5.8 x 10^{-3})	3.5 x 10^{-5}	4.5 x 10^{-4}
28	Biphenyl	(5.8 x 10^{-3})	7.6 x 10^{-6}	2.1 x 10^{-4}

[a] Parentheses indicate that no statistical data were available, so an average potency was used.

[b] A minus indicates that the chemical was not a mutagen by the test reported.

[c] A plus indicates that the chemical was positive on the test, but no numerial data were reported.

TABLE 15. RANKING OF PROBABLE CARCINOGENS BY EQUIVALENT EMISSIONS OF B(a)P AFTER 24 HOURS

Chemical	Emissions, kg/yr, remaining after 24 hours	Average mutagenic/ carcinogenic potency	Average x kg remaining after 24 hours
Benzo(a)pyrene	8.3×10^{5}[a]	1.0	8.3×10^{5}
Tetrachloroethylene	8.5×10^{7}[a]	9.0×10^{-3}	7.7×10^{5}
Ethylene dichloride	9.1×10^{7}[a]	4.1×10^{-3}	3.7×10^{5}
Benzene	5.9×10^{7}[a]	4.8×10^{-3}	2.8×10^{5}
Carbon tetrachloride	1.6×10^{7}[a]	1.2×10^{-2}	1.9×10^{5}
Vinyl chloride	3.0×10^{7}	2.7×10^{-3}	8.2×10^{4}
Trichloroethylene	1.7×10^{7}	4.3×10^{-3}	7.3×10^{4}
Chlordane	9.6×10^{6}	3.2×10^{-3}	3.1×10^{4}
Ethylene dibromide	2.1×10^{6}[b]	9.3×10^{-3}	2.0×10^{4}
Chloroform	7.2×10^{5}	1.7×10^{-2}	1.2×10^{4}
Dichlorobutene	8.7×10^{5}	4.8×10^{-3}	4.2×10^{3}
Toluene-2,4-diamine	4.4×10^{5}[a]	6.0×10^{-3}	2.6×10^{3}
DDT	1.9×10^{4}	1.5×10^{-1}	2.8×10^{3}
Dioxane	1.3×10^{6}[a]	1.9×10^{-3}	2.5×10^{3}
Acrylonitrile	3.7×10^{5}[a]	4.7×10^{-3}	1.8×10^{3}
Chlorobenzilate	9.0×10^{5}	1.9×10^{-3}	1.7×10^{3}
Heptachlor	1.1×10^{4}	1.2×10^{-1}	1.3×10^{3}
Vinylidene chloride	2.1×10^{5}	4.9×10^{-3}	1.0×10^{3}
Ethylenimine	1.7×10^{4}	2.0×10^{-2}	3.4×10^{2}
Benzyl chloride	4.1×10^{5}[a]	3.3×10^{-4}	1.4×10^{2}
Chrysene	1.7×10^{4}[a]	3.0×10^{-3}	5.1×10^{1}
Methylene bis(chloroaniline)	1.1×10^{4}	4.3×10^{-3}	4.8×10^{1}
Benzidine	3.5×10^{4}[a]	9.5×10^{-4}	3.3×10^{1}
Dichlorobenzidine	2.3×10^{3}	9.0×10^{-3}	2.1×10^{1}
Tetrachloroethane	9.4×10^{3}	2.1×10^{-3}	2.0×10^{1}
Dinitrotoluene	4.0×10^{2}	9.0×10^{-3}	3.6
Benz(a)anthracene	$<1.0 \times 10^{2}$	3.4×10^{-2}	<3.4
Diaminoanisole	1.4×10^{2}	1.4×10^{-2}	2.0
Epichlorohydrin	8.6×10^{2}	1.5×10^{-3}	1.3
Trichlorfon	1.0×10^{2}	1.3×10^{-2}	1.3
Captan	$<1.0 \times 10^{2}$	6.6×10^{-3}	$<6.6 \times 10^{-1}$
Nitrosodimethylamine	>1.0	9.6×10^{-2}	$>9.6 \times 10^{-2}$
Bis(chloromethyl) ether	<1.0	2.0×10^{-2}	$>2.0 \times 10^{-2}$
Ethyl carbamate (urethane)	4.5	3.2×10^{-3}	1.5×10^{-2}
Dimethylhydrazine	2.0	1.5×10^{-3}	3.0×10^{-3}
Hydrazine	>1.0	1.4×10^{-3}	$>1.4 \times 10^{-3}$
Aldrin (3.0×10^{6})[c]	0	5.4×10^{-2}	0
Polychlorinated biphenyls (1.7×10^{5})[c]	0	2.2×10^{-2}	0

[a] One of 20 significant carcinogens which were selected for variety of chemical type and high ranking in prioritization.

[b] As of 22 February 1979, MRC has recommended that tetraethyl lead and cumene hydroperoxide be dropped from the list of 20 and replaced by ethylene dibromide and dichloropropene.

[c] Now out of production.

TABLE 16. RANKING OF POSSIBLE CARCINOGENS BY EQUIVALENT EMISSIONS OF B(a)P AFTER 24 HOURS

Chemical	Emissions, kg/yr, remaining after 24 hours	Average mutagenic/ carcinogenic potency	Average x kg remaining after 24 hours
Pentachlorophenol	2.1×10^{7}[a]	4.0×10^{-3}	$8.x \times 10^{4}$
Dichloropropene	2.2×10^{7}[b]	3.3×10^{-3}	7.3×10^{4}
Tetraethyl lead	4.7×10^{6}[a,b]	1.1×10^{-2}	5.2×10^{4}
Methyl chloride	1.6×10^{7}	2.0×10^{-3}	3.1×10^{4}
Styrene	5.6×10^{6}[a]	3.3×10^{-3}	1.9×10^{4}
Hexachlorobutadiene	3.4×10^{6}[a]	4.8×10^{-3}	1.6×10^{4}
Chloroprene	1.3×10^{6}	9.1×10^{-3}	1.2×10^{4}
Morpholine	5.5×10^{6}	2.1×10^{-3}	1.1×10^{4}
Hexachlorobenzene	1.6×10^{5}	5.8×10^{-2}	9.4×10^{3}
1,1-Dichloroethane	2.6×10^{6}	3.3×10^{-3}	8.6×10^{3}
Di-(2-ethylhexyl) phthalate	1.2×10^{6}[a]	2.7×10^{-3}	3.3×10^{3}
Vinyl acetate	6.8×10^{5}[a]	2.5×10^{-3}	1.7×10^{3}
Allyl chloride	1.1×10^{5}	9.3×10^{-3}	1.0×10^{3}
Ethylene oxide	3.8×10^{4}[a]	3.3×10^{-3}	1.3×10^{2}
Methylenedianiline	2.6×10^{4}	2.5×10^{-3}	6.6×10^{1}
Cumene hydroproxide	8.2×10^{4}[a,b]	4.5×10^{-4}	3.7×10^{1}
Acrolein	1.1×10^{4}[a]	3.3×10^{-3}	3.6×10^{1}
Mercaptobenzothiazole	4.8×10^{3}	5.5×10^{-3}	2.6×10^{1}
Di-tert-butyl peroxide	1.1×10^{4}	1.9×10^{-3}	2.1×10^{1}
1-Naphthylamine	8.0×10^{3}	1.7×10^{-3}	1.4×10^{1}
Dichloronaphthoquinone	9.0×10^{2}	9.9×10^{-3}	8.9
Vinyl bromide	4.0×10^{3}	2.1×10^{-3}	8.4
Propylene oxide	1.7×10^{4}	4.7×10^{-4}	8.0
Dichlorovinyl dimethyl phosphate	2.0×10^{2}	4.6×10^{-3}	9.2×10^{1}
Nitrochlorobenzene	3.0×10^{2}	3.3×10^{-3}	6.6×10^{-1}
Formaldehyde	45.8	1.4×10^{-2}	6.4×10^{-1}
Trichlorophenol	5.0×10^{2}	5.9×10^{-4}	3.0×10^{-1}
Biphenyl (9.2×10^{4})	0	2.1×10^{-4}	0

[a] One of 20 significant carcinogens which were selected for variety of chemical type and high ranking in prioritization.

[b] As of 22 February 1979, MRC has recommended that tetraethyl lead and cumene hydroperoxide be dropped from the list of 20 and replaced by ethylene dibromide and dichloropropene.

SECTION 5

STATE-OF-THE-ART REVIEW OF CARCINOGENIC COFACTORS

Because a portion of this contract was to be devoted to the determination of the effects of carcinogenic cofactors, a literature search was conducted that resulted in a review of the state of the art of carcinogenic cofactors. This review concentrated on the effects of various industrial chemicals on the carcinogenic potential of other industrial chemicals. It also lightly reviewed other cofactor effects such as physiological (e.g., hormonal), genetic, medical (e.g., disease states), environmental (e.g., light), dietary, and other factors that affect the initiation or growth of cancers.

Some of the key words or word stems utilized in this computer search were: cocarcinogen... or co-carcinogen...
syncarcinogen...

Other words or word stems which were used in conjunction with carcinogen... included:
modifier...
promoter...
inhibitor...
enhances...
synergy or synergism

Among the National Library of Medicine data bases, MEDLINE, TOXLINE, CANCERLINE, and CANCERPROJ were search. On the SDC system, CHEMCON (chemical abstracts) was searched. The total number of literature citations printed off line was 2,327; the percentages from the various data files were: MEDLINE, 10%; TOXLINE, 40%; CANCERLINE, 45%, CANCERPROJ, 2%; and CHEMCON, 3%. These abstracts were reviewed along with several books and other reference papers. A summary of the "state of the art" of carcinogen cofactors is included in Appendix B, "A Review of the Carcinogen Cofactor Literature."

SECTION 6

CARCINOGEN ISOPLETH GENERATION

A portion of the effort in the first phase of this contract was to be devoted to determining the location of optimum sampling sites in four cities where field validation of the sampling and analysis equipment and techniques is to occur (Houston, Los Angeles, Birmingham, and Newark).

In order to accomplish this task, the MRC Source Assessment Data Base was used to obtain most of the necessary input for the EPA Climatological Dispersion Model (CDM).

Meterological data from the National Climatic Center (STAR computer program) were reviewed for Houston, Los Angeles, Newark, and Birmingham. These data consisted of joint frequencies of occurrence of wind direction, wind speed, and atmospheric stability (Pasquill stability classes).

It was decided that only one set of isopleths would be generated for each of the target cities and that it would include the total mass of those carcinogenic chemicals included on the MRC Source Assessment Data Base that are emitted in these cities.

This decision reflects the purpose of these particular isopleths: to aid in the selection of sampling sites to be used in evaluating the portable and high-volume sampler systems. For this purpose, the important factor is the mass of emissions, not the potency of the carcinogens.

The chemicals included in the study are from the list of probable chemical carcinogens generated earlier in the project. The probable carcinogens are generally chemicals for which animal studies have been positive, with supporting mutagenic data, or for which government regulations have been promulgated that require the chemical to be handled as a carcinogen regardless of the animal data.

The chemicals were selected from the list of probable carcinogens ordered according to annual mass of emissions released to the environment corrected for atmospheric degradation after 24 hours. From the top 30 chemicals, 19 were on the source assessment data base. Many of the other 11 chemicals are pesticides that are currently being phased out of production. The 19 chemicals selected for evaluation are shown along with the target cities in which they are found in Table 17.

TABLE 17. CHEMICALS IN TOP 30 PROBABLE CARCINOGENS ON MRC DATA BASE THAT ARE FOUND IN FOUR CITIES[a]

Compound	Houston	Newark	Los Angeles	Birmingham
Ethylene dichloride	X		X	
Ethylene dibromide	X			
Vinyl chloride	X	X	X	
Chloroform	X	X	X	
Carbon tetrachloride	X	X	X	
Vinylidene chloride	X	X	X	
Benzene	X	X	X	
Acrylonitrile	X	X	X	
Dichlorobutene	X			
Trichloroethylene	X			
Tetrachloroethane	X			
Epichlorohydrin		X		
Benzyl chloride		X		
Polyvinylidene		X		
DDT			X	

[a] From annual emissions in the United States that remain after 24 hours.

All sources of emission were located on maps in Universal Transverse Mercator (UTM) coordinates for the four cities. The input data were gathered and keypunched. The conversion from street addresses to UTM coordinates were more difficult and time consuming than originally estimated. The Houston area was selected for the first simulated dispersion modeling.

Annual meterological data (from the STAR computer program [19] for Houston were initially used with a coarse grid of about 50 x 50 km (in about 2-km intervals) with approximately 625 receptor points. The average stack heights used were as listed in the MRC Source Assessment Data Base (SADB) [1]. Annual production rates and emission factors were also from the SADB.

---

[19] Seasonal & Annual (Day/Night) Wind Distribution by Pasquill Stability Classes (6), STAR Program. U.S. Department of Commerce, National Oceanic and Atmospheric Administration, Environmental Data Service, National Climatic Center, Asheville, North Carolina, July 15, 1977.

Average mixing depths were from a paper by Holzworth [20]. The average annual Houston temperature of 21.11°C was from the Statistical Abstract of the United States [21]. A stack diameter of 0.30 m was estimated by MRC personnel. Exit velocities for given stack diameters and flow rates were found for a typical process [22, 23]. A gas exit temperature of 38°C was assumed. Environmental persistence was assumed to be a 1-week half-life (essentially nondegrading for this model). The appropriate maximum was located; then the area around the maximum was "fine tuned" and rerun for the final isopleth to be plotted. A three-dimensional concentration isopleth was made.

Along with the other sources of pollution, there were eight point sources for ethylene dichloride and five for vinyl chloride in the Houston area. All were located in Deer Park and Pasadena, southwest of Houston. The companies from which the emissions occur are primarily Shell Chemical Company, Ethyl Corporation, and Diamond Shamrock Company.

A preliminary computer run was conducted using only the ethylene dichloride and vinyl chloride data for Houston. The EPA CDM [24] was used for the computerized analysis. Initial results with a relatively coarse grid show the maximum total pollution about 1 km north of the Shell plant. A map of this area with a ground-level isopleth of 500 $\mu g/m^3$ for ethylene dichloride is shown in Figure 1. Listings of the CDM input parameters and computer output are shown in Figures 2 and 3.

In the parameters on the first sheet of Figure 2, sigma Z is the standard deviation of the vertical wind profile. The joint frequency function indicates the wind direction and stability class

---

[20] Holzworth, G. C. Estimates of Mean Maximum Mixing Depths in the Contiguous United States. Monthly Weather Review, 92(5):235-242, 1964.

[21] Statistical Abstract of the United States, 97th Edition. U.S. Bureau of the Census, Washington, D.C., 1976. p. 161.

[22] Khan, Z. S., and T. W. Hughes. Source Assessment: Polyvinyl Chloride. EPA-600/2-78-004i, U.S. Environmental Protection Agency, Cincinnati, Ohio, May 1978. 105 pp.

[23] Scientific and Technical Assessment Report on Vinyl Chloride and Polyvinyl Chloride. EPA-600/6-75-004, U.S. Environmental Protection Agency, Washington, D.C., December 1975. 130 pp.

[24] Busse, A. D., and J. R. Zimmerman. User's Guide for the Flimatological Dispersion Model. EPA-R4-73-024, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, December 1973. 144 pp.

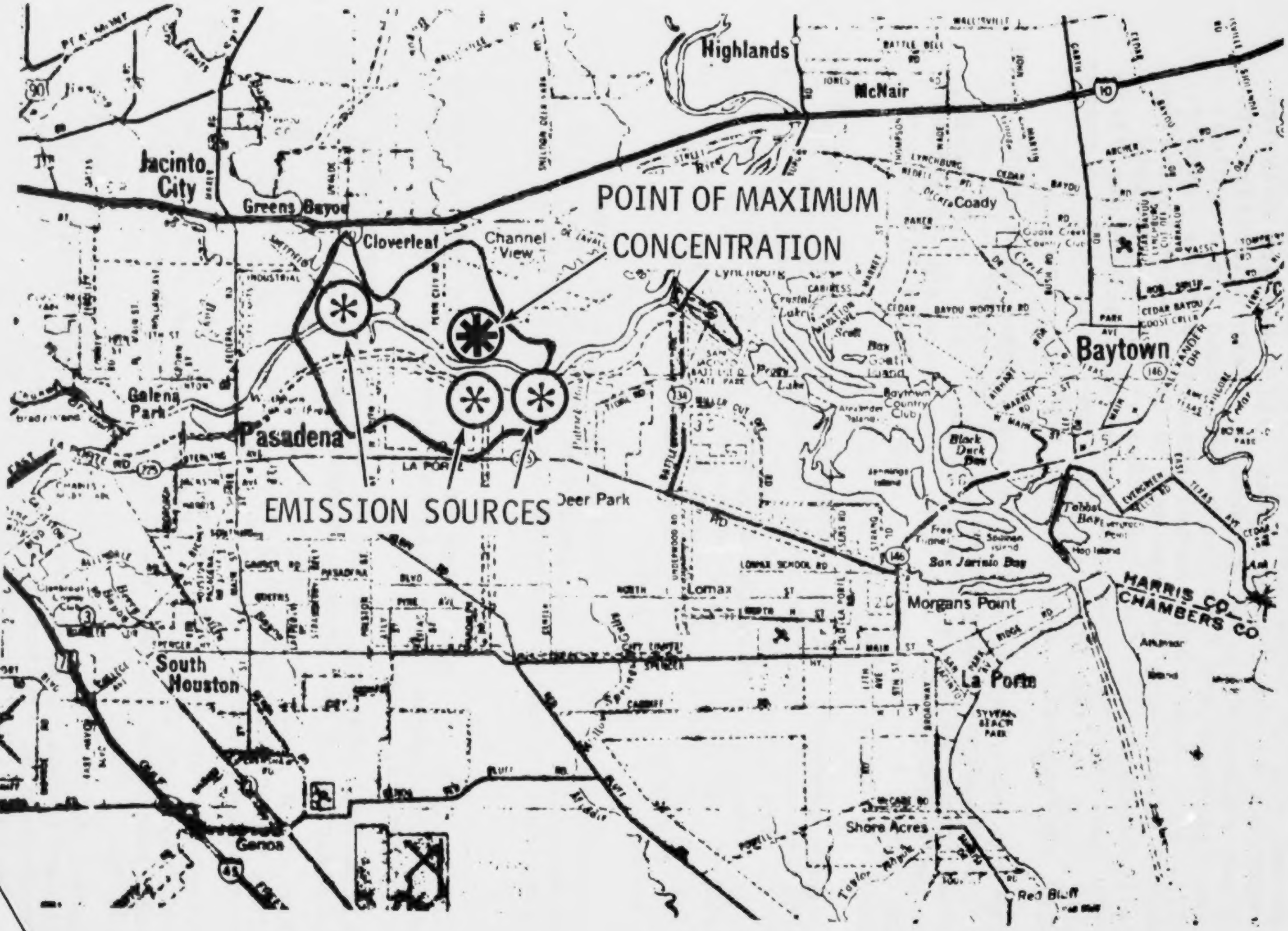

POINT OF MAXIMUM
CONCENTRATION
EMISSION SOURCES
Highlands
McNair
Jacinto City
Greens Bayou
Cloverleaf
Channel View
Coady
Lynchburg
Baytown
Galena Park
Pasadena
Deer Park
Baytown Country Club
Black Duck Bay
San Jacinto Bay
Lomax
Morgans Point
HARRIS CO.
CHAMBERS CO
La Porte
South Houston
Genoa
Shore Acres
Red Bluff

Figure 1. Ethylene dichloride concentrations in Houston, Texas at 500 $\mu g/m^3$ (3 km/cm).

Reproduced from best available copy.

```
                                        CDM VERSION 74114,  RUN     4
THE CENTRAL WIND SPEEDS OF THE SIX WIND SPEED CLASSES (U):
       0.150000E+01         0.245872E+01         0.447040E+01         0.692912E+01         0.961136E+01         0.125171E+02

THE EXPONENTIAL OF THE VERTICAL WIND PROFILE BY STABILITY CLASS (UE):
       0.100000E+00         0.150000E+00         0.200000E+00         0.250000E+00         0.250000E+00         0.300000E+00

THE INITIAL SIGMA Z FOR AREA SOURCES BY STABILITY CLASS (SZA):
       0.0                  0.0                  0.0                  0.0                  0.0                  0.0

THE CLIMATOLOGICAL MEAN NOCTURNAL AND AFTERNOON MIXING HEIGHTS (HMIN,HT):
       0.198000E+03         0.992000E+03

THE DAY AND NIGHT EMISSION WEIGHT FACTORS (YD,YN):
       0.100000E+01         0.100000E+01

THE X-MIN AND Y-MIN OF THE AREA EMISSION INVENTORY GRID (XG,YG):
       0.880000E+02         0.870000E+02

THE WIDTH OF A BASIC AREA SOURCE SQUARE (TXX):
       0.100000E+04

THE NUMBER OF SUB-SECTORS CONSIDERED IN A 22.5 DEGREE SECTOR, AND ANGULAR WIDTH OF A SUB-SECTOR (DINT,THETA):
       0.400000E+01         0.562500E+01

THE INITIAL RADIAL INCREMENT (DELR):
       0.250000E+03

THE RADIAL INCREMENT FACTORS (INC):
                 1                    2                    4                    4

THE RATIO OF EMISSION GRID TO MAP GRID (RAT):
       0.400000E+01

THE GRID CONVERSION FACTOR (CV):
       0.250000E+03

THE AMBIENT AIR TEMPERATURE (TOA):
       0.295160E+03

THE DECAY RATE HALF LIFE FOR P 1 AND P 2 (GB):
       0.234000E+03         0.120000E+02

THE SIGMA Z COEFFICIENT TABLE (G):
       0.253900E-03         0.253900E-03         0.383000E-01         0.208860E+01         0.208860E+01         0.128120E+01
       0.493600E-01         0.493600E-01         0.139300E+00         0.111370E+01         0.111370E+01         0.946700E+00
       0.115400E+00         0.101400E+00         0.112000E+00         0.910900E+00         0.926000E+00         0.910000E+00
       0.736800E+00         0.259100E+00         0.856000E-01         0.564200E+00         0.686900E+00         0.865000E+00
       0.129690E+01         0.252700E+00         0.818000E-01         0.442100E+00         0.634100E+00         0.815500E+00
```

(continued)

Figure 2. Input data.

```
                                         CDM VERSION 74114,  RUN     4
           U1                  U2                  U3                  U4                  U5                  U6
SECTOR

                                         THE JOINT FREQUENCY FUNCTION FOR STABILITY CLASS  1

   1       0.460000E-03        0.250000E-03        0.0                 0.0                 0.0                 0.0
   2       0.280000E-03        0.270000E-03        0.0                 0.0                 0.0                 0.0
   3       0.320000E-03        0.210000E-03        0.0                 0.0                 0.0                 0.0
   4       0.510000E-03        0.370000E-03        0.0                 0.0                 0.0                 0.0
   5       0.129000E-02        0.730000E-03        0.0                 0.0                 0.0                 0.0
   6       0.540000E-03        0.600000E-03        0.0                 0.0                 0.0                 0.0
   7       0.880000E-03        0.550000E-03        0.0                 0.0                 0.0                 0.0
   8       0.800000E-03        0.570000E-03        0.0                 0.0                 0.0                 0.0
   9       0.118000E-02        0.126000E-02        0.0                 0.0                 0.0                 0.0
  10       0.780000E-03        0.390000E-03        0.0                 0.0                 0.0                 0.0
  11       0.630000E-03        0.640000E-03        0.0                 0.0                 0.0                 0.0
  12       0.680000E-03        0.530000E-03        0.0                 0.0                 0.0                 0.0
  13       0.710000E-03        0.530000E-03        0.0                 0.0                 0.0                 0.0
  14       0.270000E-03        0.250000E-03        0.0                 0.0                 0.0                 0.0
  15       0.380000E-03        0.140000E-03        0.0                 0.0                 0.0                 0.0
  16       0.450000E-03        0.210000E-03        0.0                 0.0                 0.0                 0.0

                                         THE JOINT FREQUENCY FUNCTION FOR STABILITY CLASS  2

   1       0.224000E-02        0.179000E-02        0.800000E-03        0.0                 0.0                 0.0
   2       0.204000E-02        0.172000E-02        0.760000E-03        0.0                 0.0                 0.0
   3       0.219000E-02        0.167000E-02        0.980000E-03        0.0                 0.0                 0.0
   4       0.237000E-02        0.206000E-02        0.112000E-02        0.0                 0.0                 0.0
   5       0.321000E-02        0.341000E-02        0.286000E-02        0.0                 0.0                 0.0
   6       0.245000E-02        0.311000E-02        0.220000E-02        0.0                 0.0                 0.0
   7       0.226000E-02        0.252000E-02        0.172000E-02        0.0                 0.0                 0.0
   8       0.212000E-02        0.261000E-02        0.135000E-02        0.0                 0.0                 0.0
   9       0.319000E-02        0.332000E-02        0.298000E-02        0.0                 0.0                 0.0
  10       0.205000E-02        0.195000E-02        0.940000E-03        0.0                 0.0                 0.0
  11       0.132000E-02        0.163000E-02        0.105000E-02        0.0                 0.0                 0.0
  12       0.139000E-02        0.188000E-02        0.115000E-02        0.0                 0.0                 0.0
  13       0.178000E-02        0.208000E-02        0.800000E-03        0.0                 0.0                 0.0
  14       0.980000E-03        0.460000E-03        0.230000E-03        0.0                 0.0                 0.0
  15       0.940000E-03        0.730000E-03        0.270000E-03        0.0                 0.0                 0.0
  16       0.980000E-03        0.137000E-02        0.550000E-03        0.0                 0.0                 0.0

                                         THE JOINT FREQUENCY FUNCTION FOR STABILITY CLASS  3

   1       0.700000E-03        0.231000E-02        0.360000E-02        0.370000E-03        0.200000E-04        0.0
   2       0.520000E-03        0.135000E-02        0.316000E-02        0.440000E-03        0.200000E-04        0.0
   3       0.105000E-02        0.229000E-02        0.369000E-02        0.270000E-03        0.0                 0.0
   4       0.900000E-03        0.174000E-02        0.357000E-02        0.140000E-03        0.0                 0.0
   5       0.107000E-02        0.309000E-02        0.822000E-02        0.920000E-03        0.0                 0.0
   6       0.115000E-02        0.273000E-02        0.673000E-02        0.890000E-03        0.0                 0.0
   7       0.103000E-02        0.298000E-02        0.609000E-02        0.640000E-03        0.0                 0.0
   8       0.960000E-03        0.243000E-02        0.696000E-02        0.147000E-02        0.0                 0.0
   9       0.127000E-02        0.334000E-02        0.123200E-01        0.252000E-02        0.140000E-03        0.0
  10       0.490000E-03        0.121000E-02        0.318000E-02        0.440000E-03        0.200000E-04        0.0
  11       0.400000E-03        0.820000E-03        0.220000E-02        0.210000E-03        0.0                 0.0
  12       0.440000E-03        0.124000E-02        0.190000E-02        0.180000E-03        0.0                 0.0
  13       0.650000E-03        0.149000E-02        0.277000E-02        0.270000E-03        0.0                 0.0
  14       0.360000E-03        0.890000E-03        0.103000E-02        0.250000E-03        0.200000E-04        0.0
  15       0.280000E-03        0.870000E-03        0.169000E-02        0.160000E-03        0.0                 0.0
  16       0.490000E-03        0.121000E-02        0.179000E-02        0.250000E-03        0.0                 0.0
```

(continued)

Figure 2 (continued)

```
                                        COM VERSION 74114,  RUN     4
            U1                 U2                 U3                 U4                 U5                 U6
SECTOR

                                        THE JOINT FREQUENCY FUNCTION FOR STABILITY CLASS  4

  1        0.780000E-03       0.268000E-02       0.630000E-02       0.792000E-02       0.890000E-03       0.180000E-03
  2        0.550000E-03       0.192000E-02       0.458000E-02       0.382000E-02       0.300000E-03       0.0
  3        0.610000E-03       0.250000E-02       0.419000E-02       0.259000E-02       0.700000E-04       0.0
  4        0.780000E-03       0.245000E-02       0.421000E-02       0.222000E-02       0.270000E-03       0.0
  5        0.103000E-02       0.389000E-02       0.824000E-02       0.621000E-02       0.530000E-03       0.500000E-04
  6        0.700000E-03       0.289000E-02       0.699000E-02       0.683000E-02       0.690000E-03       0.0
  7        0.590000E-03       0.282000E-02       0.554000E-02       0.412000E-02       0.530000E-03       0.200000E-04
  8        0.630000E-03       0.291000E-02       0.786000E-02       0.994000E-02       0.940000E-03       0.200000E-04
  9        0.870000E-03       0.334000E-02       0.127100E-01       0.184400E-01       0.204000E-02       0.230000E-03
 10        0.280000E-03       0.149000E-02       0.284000E-02       0.364000E-02       0.300000E-03       0.0
 11        0.360000E-03       0.800000E-03       0.160000E-02       0.131000E-02       0.180000E-03       0.0
 12        0.200000E-03       0.980000E-03       0.920000E-03       0.760000E-03       0.200000E-04       0.0
 13        0.250000E-03       0.124000E-02       0.144000E-02       0.128000E-02       0.180000E-03       0.110000E-03
 14        0.260000E-03       0.600000E-03       0.760000E-03       0.124000E-02       0.210000E-03       0.140000E-03
 15        0.220000E-03       0.890000E-03       0.181000E-02       0.273000E-02       0.101000E-02       0.140000E-03
 16        0.270000E-03       0.119000E-02       0.302000E-02       0.481000E-02       0.142000E-02       0.500000E-04

                                        THE JOINT FREQUENCY FUNCTION FOR STABILITY CLASS  5

  1        0.230000E-02       0.279000E-02       0.905000E-02       0.870000E-02       0.103000E-02       0.900000E-04
  2        0.189000E-02       0.227000E-02       0.547000E-02       0.263000E-02       0.230000E-03       0.0
  3        0.242000E-02       0.222000E-02       0.460000E-02       0.140000E-02       0.900000E-04       0.200000E-04
  4        0.197000E-02       0.195000E-02       0.339000E-02       0.105000E-02       0.110000E-03       0.0
  5        0.370000E-02       0.426000E-02       0.628000E-02       0.199000E-02       0.160000E-03       0.700000E-04
  6        0.236000E-02       0.270000E-02       0.740000E-02       0.311000E-02       0.210000E-03       0.250000E-03
  7        0.220000E-02       0.295000E-02       0.728000E-02       0.218000E-02       0.110000E-03       0.200000E-04
  8        0.308000E-02       0.346000E-02       0.106300E-01       0.497000E-02       0.230000E-03       0.700000E-04
  9        0.382000E-02       0.483000E-02       0.119100E-01       0.453000E-02       0.900000E-04       0.200000E-04
 10        0.101000E-02       0.920000E-03       0.227000E-02       0.410000E-03       0.200000E-04       0.0
 11        0.660000E-03       0.480000E-03       0.890000E-03       0.210000E-03       0.0                0.0
 12        0.350000E-03       0.440000E-03       0.480000E-03       0.320000E-03       0.200000E-04       0.0
 13        0.550000E-03       0.500000E-03       0.620000E-03       0.320000E-03       0.200000E-04       0.0
 14        0.390000E-03       0.480000E-03       0.500000E-03       0.780000E-03       0.140000E-03       0.230000E-03
 15        0.620000E-03       0.440000E-03       0.147000E-02       0.174000E-02       0.410000E-03       0.110000E-03
 16        0.960000E-03       0.124000E-02       0.360000E-02       0.497000E-02       0.112000E-02       0.160000E-03

                                        THE JOINT FREQUENCY FUNCTION FOR STABILITY CLASS  6

  1        0.265600E-01       0.124600E-01       0.511000E-02       0.0                0.0                0.0
  2        0.178000E-01       0.694000E-02       0.115000E-02       0.0                0.0                0.0
  3        0.154200E-01       0.719000E-02       0.850000E-03       0.0                0.0                0.0
  4        0.108500E-01       0.447000E-02       0.300000E-03       0.0                0.0                0.0
  5        0.154900E-01       0.600000E-02       0.550000E-03       0.0                0.0                0.0
  6        0.147200E-01       0.623000E-02       0.149000E-02       0.0                0.0                0.0
  7        0.275600E-01       0.112900E-01       0.183000E-02       0.0                0.0                0.0
  8        0.343200E-01       0.152100E-01       0.346000E-02       0.0                0.0                0.0
  9        0.452600E-01       0.168300E-01       0.396000E-02       0.0                0.0                0.0
 10        0.108800E-01       0.364000E-02       0.820000E-03       0.0                0.0                0.0
 11        0.670000E-02       0.236000E-02       0.690000E-03       0.0                0.0                0.0
 12        0.662000E-02       0.247000E-02       0.230000E-03       0.0                0.0                0.0
 13        0.985000E-02       0.279000E-02       0.660000E-03       0.0                0.0                0.0
 14        0.472000E-02       0.208000E-02       0.530000E-03       0.0                0.0                0.0
 15        0.564000E-02       0.250000E-02       0.133000E-02       0.0                0.0                0.0
 16        0.101600E-01       0.495000E-02       0.268000E-02       0.0                0.0                0.0
```

(continued)

Figure 2 (continued)

```
                                          CDM VERSION 74114,  RUN     4
SOURCE INPUT
      X            Y                TX          S1           S2           SH           D            VS           T                 SA
  0.90000E+02  0.92000E+02  0.0             0.14000E+02  0.83000E+01  0.45700E+02  0.16000E+01  0.90000E-01  0.38000E+02  0.0
  0.90000E+02  0.92000E+02  0.0             0.12810E+03  0.0          0.30500E+02  0.10000E+01  0.15000E+01  0.38000E+02  0.0
  0.90000E+02  0.92000E+02  0.0             0.52210E+02  0.0          0.27400E+02  0.10000E+01  0.14300E+01  0.38000E+02  0.0
  0.94000E+02  0.90000E+02  0.0             0.73400E+01  0.46700E+02  0.45700E+02  0.16000E+01  0.94000E-01  0.38000E+02  0.0
  0.94000E+02  0.90000E+02  0.0             0.64800E+02  0.0          0.30500E+02  0.10000E+01  0.15000E+01  0.38000E+02  0.0
  0.94000E+02  0.90000E+02  0.0             0.29200E+03  0.0          0.27400E+02  0.10000E+01  0.15000E+01  0.38000E+02  0.0
  0.96000E+02  0.90000E+02  0.0             0.23800E+02  0.0          0.30500E+02  0.10000E+01  0.15000E+01  0.38000E+02  0.0
  0.96000E+02  0.90000E+02  0.0             0.66800E+02  0.0          0.27400E+02  0.10000E+01  0.14300E+01  0.38000E+02  0.0
  0.90000E+02  0.92000E+02  0.0             0.0          0.72000E-05  0.12200E+02  0.50000E+00  0.57500E+01  0.38000E+02  0.0
  0.94000E+02  0.90000E+02  0.0             0.0          0.40000E-04  0.12200E+02  0.50000E+00  0.57500E+01  0.38000E+02  0.0
  0.96000E+02  0.90000E+02  0.0             0.0          0.92000E-05  0.12200E+02  0.50000E+00  0.57500E+01  0.38000E+02  0.0

        0 AREA SOURCES.        11 POINT SOURCES.
```

Figure 2 (continued)

```
                                          CDM VERSION 74114,  RUN     4
                                          (MICROGRAMS PER CUBIC METER)
                               AREA                 POINT                  TOTAL                CALIBRATED             OBSERVED
  COORDINATES              P 1        P 2        P 1        P 2        P 1        P 2        P 1        P 2        P 1        P 2
 88.00      87.00          0.         0.        189.        11.       189.        11.       189.        11.         0          1
 88.00      88.00          0.         0.        125.         8.       125.         8.       125.         8.         0          1
 88.00      89.00          0.         0.        336.        19.       336.        19.       336.        19.         0          1
 88.00      90.00          0.         0.        370.        19.       370.        19.       370.        19.         0          1
 88.00      91.00          0.         0.        376.        19.       376.        19.       376.        19.         0          1
 88.00      92.00          0.         0.        496.        18.       496.        18.       496.        18.         0          1
 88.00      93.00          0.         0.        415.        17.       415.        17.       415.        17.         0          1
 88.00      94.00          0.         0.        409.        17.       409.        17.       409.        17.         0          1
 89.00      87.00          0.         0.        220.        13.       220.        13.       220.        13.         0          1
 89.00      88.00          0.         0.        258.        14.       258.        14.       258.        14.         0          1
 89.00      89.00          0.         0.        326.        15.       326.        15.       326.        15.         0          1
 89.00      90.00          0.         0.        481.        22.       481.        22.       481.        22.         0          1
 89.00      91.00          0.         0.        586.        20.       586.        20.       586.        20.         0          1
 89.00      92.00          0.         0.        876.        20.       876.        20.       876.        20.         0          1
 89.00      93.00          0.         0.        734.        19.       734.        19.       734.        19.         0          1
 89.00      94.00          0.         0.        653.        24.       653.        24.       653.        24.         0          1
 89.00      95.00          0.         0.        498.        22.       498.        22.       498.        22.         0          0
 89.00      96.00          0.         0.        397.        20.       397.        20.       397.        20.         0          0
 90.00      87.00          0.         0.        339.        19.       339.        19.       339.        19.         0          1
 90.00      88.00          0.         0.        367.        17.       367.        17.       367.        17.         0          1
 90.00      89.00          0.         0.        476.        18.       476.        18.       476.        18.         0          1
 90.00      90.00          0.         0.        731.        27.       731.        27.       731.        27.         0          1
 90.00      91.00          0.         0.       1074.        22.      1074.        22.      1074.        22.         0          1
 90.00      92.00          0.         0.        262.        18.       262.        18.       262.        18.         0          1
 90.00      93.00          0.         0.       1572.        27.      1572.        27.      1572.        27.         0          1
 90.00      94.00          0.         0.        900.        28.       900.        28.       900.        28.         0          1
 90.00      95.00          0.         0.        647.        26.       647.        26.       647.        26.         0          0
 90.00      96.00          0.         0.        547.        28.       547.        28.       547.        28.         0          0
 91.00      87.00          0.         0.        301.        18.       301.        18.       301.        18.         0          1
 91.00      88.00          0.         0.        317.        17.       317.        17.       317.        17.         0          1
 91.00      89.00          0.         0.        380.        18.       380.        18.       380.        18.         0          1
 91.00      90.00          0.         0.        625.        28.       625.        28.       625.        28.         0          1
 91.00      91.00          0.         0.        541.        24.       541.        24.       541.        24.         0          1
 91.00      92.00          0.         0.        635.        23.       635.        23.       635.        23.         0          1
 91.00      93.00          0.         0.        522.        26.       522.        26.       522.        26.         0          1
 91.00      94.00          0.         0.        465.        25.       465.        25.       465.        25.         0          1
 91.00      95.00          0.         0.        424.        27.       424.        27.       424.        27.         0          0
 91.00      96.00          0.         0.        341.        24.       341.        24.       341.        24.         0          0
 92.00      87.00          0.         0.        376.        20.       376.        20.       376.        20.         0          1
 92.00      88.00          0.         0.        457.        21.       457.        21.       457.        21.         0          1
 92.00      89.00          0.         0.        499.        19.       499.        19.       499.        19.         0          1
 92.00      90.00          0.         0.        810.        29.       810.        29.       810.        29.         0          1
 92.00      91.00          0.         0.        659.        25.       659.        25.       659.        25.         0          1
 92.00      92.00          0.         0.        729.        31.       729.        31.       729.        31.         0          1
 92.00      93.00          0.         0.        680.        36.       680.        36.       680.        36.         0          1
 92.00      94.00          0.         0.        521.        32.       521.        32.       521.        32.         0          1
 92.00      95.00          0.         0.        444.        29.       444.        29.       444.        29.         0          0
 92.00      96.00          0.         0.        370.        25.       370.        25.       370.        25.         0          0
 93.00      87.00          0.         0.        421.        20.       421.        20.       421.        20.         0          1
 93.00      88.00          0.         0.        558.        20.       558.        20.       558.        20.         0          1
```

(continued)

Figure 3. Output data.

```
                                         CDM VERSION 74114.  RUN     4
                                        (MICROGRAMS PER CUBIC METER)
                            AREA                 POINT                 TOTAL                 CALIBRATED            OBSERVED
   COORDINATES         P 1         P 2         P 1        P 2        P 1        P 2        P 1        P 2       P 1        P 2
  93.00     89.00       0.          0.         853.       17.        853.       17.        853.       17.        0          1
  93.00     90.00       0.          0.        1570.       24.       1570.       24.       1570.       24.        0          1
  93.00     91.00       0.          0.        1281.       24.       1281.       24.       1281.       24.        0          1
  93.00     92.00       0.          0.        1053.       36.       1053.       36.       1053.       36.        0          1
  93.00     93.00       0.          0.         741.       36.        741.       36.        741.       36.        0          1
  93.00     94.00       0.          0.         559.       33.        559.       33.        559.       33.        0          0
  93.00     95.00       0.          0.         454.       29.        454.       29.        454.       29.        0          0
  93.00     96.00       0.          0.         445.       33.        445.       33.        445.       33.        0          0
  94.00     85.00       0.          0.         354.       24.        354.       24.        354.       24.        0          0
  94.00     86.00       0.          0.         462.       28.        462.       28.        462.       28.        0          0
  94.00     87.00       0.          0.         617.       29.        617.       29.        617.       29.        0          1
  94.00     88.00       0.          0.         939.       27.        939.       27.        939.       27.        0          1
  94.00     89.00       0.          0.        1810.       14.       1810.       14.       1810.       14.        0          1
  94.00     90.00       0.          0.         197.        1.        197.        1.        197.        1.        0          1
  94.00     91.00       0.          0.        2908.       27.       2908.       27.       2908.       27.        0          1
  94.00     92.00       0.          0.        1523.       47.       1523.       47.       1523.       47.        0          1
  94.00     93.00       0.          0.        1013.       48.       1013.       48.       1013.       48.        0          1
  94.00     94.00       0.          0.         729.       44.        729.       44.        729.       44.        0          0
  94.00     95.00       0.          0.         560.       38.        560.       38.        560.       38.        0          0
  94.00     96.00       0.          0.         444.       33.        444.       33.        444.       33.        0          0
  95.00     87.00       0.          0.         315.       13.        315.       13.        315.       13.        0          1
  95.00     88.00       0.          0.         462.       14.        462.       14.        462.       14.        0          1
  95.00     89.00       0.          0.         507.        7.        507.        7.        507.        7.        0          1
  95.50     89.50       0.          0.         600.        7.        600.        7.        600.        7.        0          0
  95.00     90.00       0.          0.         989.       12.        989.       12.        989.       12.        0          1
  95.50     90.00       0.          0.        1129.       13.       1129.       13.       1129.       13.        0          0
  95.50     90.50       0.          0.         873.       11.        873.       11.        873.       11.        0          0
  95.00     91.00       0.          0.         637.       11.        637.       11.        637.       11.        0          1
  95.50     91.00       0.          0.         743.       12.        743.       12.        743.       12.        0          0
  95.00     92.00       0.          0.         571.       15.        571.       15.        571.       15.        0          1
  95.00     93.00       0.          0.         383.       14.        383.       14.        383.       14.        0          1
  95.00     94.00       0.          0.         284.       12.        284.       12.        284.       12.        0          1
  95.00     96.00       0.          0.         465.       32.        465.       32.        465.       32.        0          0
  96.00     87.00       0.          0.         336.       13.        336.       13.        336.       13.        0          1
  96.00     88.00       0.          0.         359.        8.        359.        8.        359.        8.        0          1
  96.00     89.00       0.          0.         575.        7.        575.        7.        575.        7.        0          1
  96.50     89.50       0.          0.         287.        7.        287.        7.        287.        7.        0          0
  96.00     90.00       0.          0.         300.       13.        300.       13.        300.       13.        0          1
  96.50     90.00       0.          0.         541.       13.        541.       13.        541.       13.        0          0
  96.50     90.50       0.          0.         344.       10.        344.       10.        344.       10.        0          0
  96.00     91.00       0.          0.         905.       11.        905.       11.        905.       11.        0          1
  96.50     91.50       0.          0.         277.       10.        277.       10.        277.       10.        0          0
  96.00     92.00       0.          0.         512.       10.        512.       10.        512.       10.        0          1
  96.00     93.00       0.          0.         419.       13.        419.       13.        419.       13.        0          1
  96.00     94.00       0.          0.         301.       11.        301.       11.        301.       11.        0          1
  97.00     87.00       0.          0.         153.        7.        153.        7.        153.        7.        0          1
  97.00     88.00       0.          0.         171.        6.        171.        6.        171.        6.        0          1
  97.00     89.00       0.          0.         179.        6.        179.        6.        179.        6.        0          1
  97.00     90.00       0.          0.         341.       12.        341.       12.        341.       12.        0          1
  97.00     91.00       0.          0.         228.        9.        228.        9.        228.        9.        0          1
```

(continued)

Figure 3 (continued)

```
                                          CDM VERSION 74114,  RUN    4
                                         (MICROGRAMS PER CUBIC METER)
                                AREA                 POINT                 TOTAL            CALIBRATED            OBSERVED
  COORDINATES                P 1       P 2       P 1       P 2       P 1       P 2       P 1       P 2       P 1       P 2
   97.00     92.00            0.        0.      207.        9.      207.        9.      207.        9.        0         1
   97.00     93.00            0.        0.      165.        8.      165.        8.      165.        8.        0         1
   97.00     94.00            0.        0.      126.        7.      126.        7.      126.        7.        0         1
   98.00     87.00            0.        0.      125.        6.      125.        6.      125.        6.        0         1
   98.00     88.00            0.        0.      104.        5.      104.        5.      104.        5.        0         1
   98.00     89.00            0.        0.      111.        5.      111.        5.      111.        5.        0         1
   98.00     90.00            0.        0.      204.       10.      204.       10.      204.       10.        0         1
   98.00     91.00            0.        0.      154.        8.      154.        8.      154.        8.        0         1
   98.00     92.00            0.        0.      135.        7.      135.        7.      135.        7.        0         1
   98.00     93.00            0.        0.      137.        7.      137.        7.      137.        7.        0         1
   98.00     94.00            0.        0.      107.        6.      107.        6.      107.        6.        0         1
   99.00     89.00            0.        0.       83.        5.       83.        5.       83.        5.        0         0
   99.00     90.00            0.        0.      144.        8.      144.        8.      144.        8.        0         0
   99.00     91.00            0.        0.      114.        6.      114.        6.      114.        6.        0         0
  100.00     89.00            0.        0.       96.        7.       96.        7.       96.        7.        0         0
  100.00     90.00            0.        0.      110.        7.      110.        7.      110.        7.        0         0
  100.00     91.00            0.        0.      109.        7.      109.        7.      109.        7.        0         0
  101.00     89.00            0.        0.       77.        6.       77.        6.       77.        6.        0         0
  101.00     90.00            0.        0.       94.        6.       94.        6.       94.        6.        0         0
  101.00     91.00            0.        0.       88.        6.       88.        6.       88.        6.        0         0
```

Figure 3 (continued)

as a fraction of the average total for a year. The compass is divided into 16 sectors beginning with 1 for north by northeast around to 16 for north. The source input X and Y coordinate parameters are taken from topographic maps and are in kilometers. S1 and S2 are point source emission rates for ethylene dichloride and vinyl chloride, respectively. SH is stack height in meters, D is stack diameter in meters, VS is exit velocity of the effluent, and T is average ambient temperature in degrees centigrade.

The output data show the ground-level concentrations of ethylene dichloride and vinyl chloride respectively, as P1 and P2. The X and Y coordinates correspond to those in the input. Any number of receptor locations (points where a computed concentration is requested) may be used. The output coordinates have been used to plot the isopleth in Figure 1 for ethylene dichloride.

Two variables unknown at the time if isopleth generation for these sources were the temperature of the gases leaving the stacks and the exit velocity of these gases. A comparison of isopleths generated at 38°C and 300°C showed the location of maximum concentration at the same point, but the 500-$\mu g/m^3$ isopleth shifted outward by about half a kilometer at the higher temperature. Discussions with plant personnel in the Houston area indicated that scrubbers are used in most of the plant, which would suggest that the lower temperature is more realistic. Different exit velocities were used to determine that the model is not sensitive to this input.

At this point, a tape of the recently improved CDM computer program was received; it was utilized in the rest of this study.

The rest of the input data for Houston were gathered for all of the probable carcinogens indicated, and the computerized CDM was run. The results were plotted and a three-dimensional model was assembled. The results are shown in Figure 4. Three different locations were found to have similar, high concentrations of carcinogens. These areas were located on a map of Houston as shown in Figure 5.

At the three points of maximum carcinogen concentration, the composition and concentration of each component carcinogenic chemical was determined. Results are displayed in Table 18. These are the prime locations to be sampled in the third phase of this contract and contract 68-02-2774 (portable carcinogen tester).

Similar data are being generated for the other cities of interest.

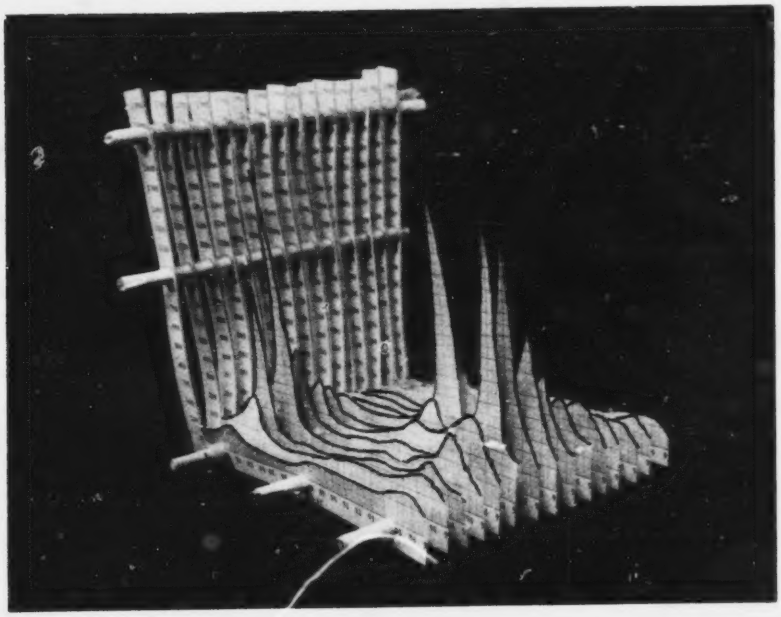


Figure 4. Houston carcinogen isopleth.

TABLE 18. AVERAGE CONCENTRATIONS AT POINTS OF MAXIMUM POLLUTION IN HOUSTON
[Micrograms per cubic meter]

Compound	82,88	90,92	95,90
Acrylonitrile	1.0	0.1	0.1
Benzene	1,366.0	6.0	5.0
Carbon tetrachloride	6.0	190.0	251.0
Chloroform	2.0	92.0	123.0
Dichlorobutene	1.0	0.02	0.02
Ethylene dichloride	26.0	977.0	757.0
Tetrachloroethane	0.009	0.022	0.018
Epichlorohydrin	0.15	1.0	1.0
Trichloroethylene	5.0	12.0	10.0
Vinyl chloride	7.0	15.0	2.0
Vinilydene chloride	0.004	0.165	0.220
Ethylene dibromide	0.14	0.01	0.10

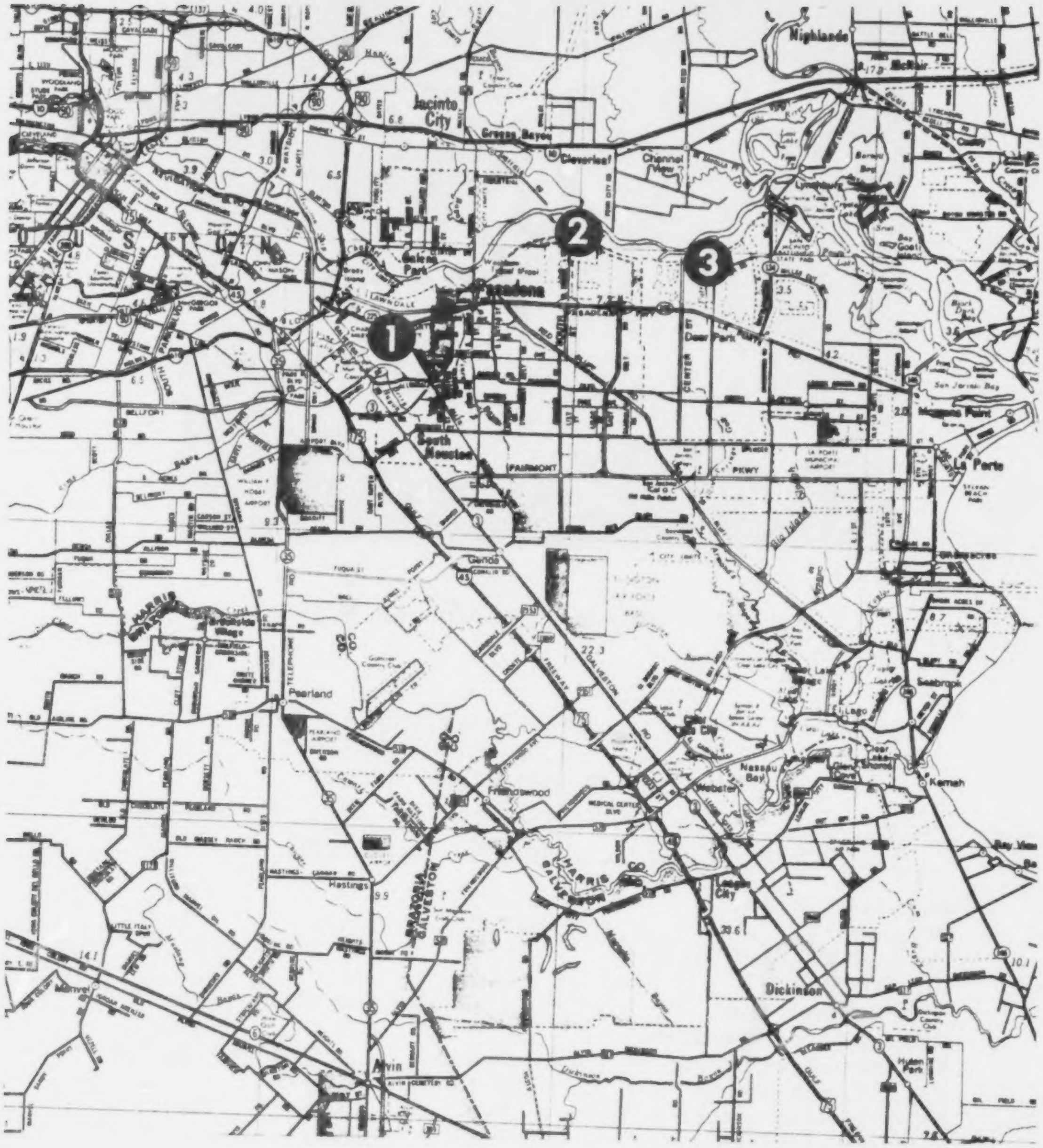

1
2
3
Highlands
Jacinto City
Cloverleaf
Channel View
Pasadena
Deer Park
South Houston
La Porte
Pearland
Friendswood
Webster
Nassau Bay
Seabrook
Kemah
League City
Dickinson
Hastings
Manvel
Alvin

Figure 5. Locations of maximum concentration of pollutants in Houston.

REFERENCES

1. Eimutis, E. C., and R. P. Quill. Source Assessment: Noncriteria Pollutant Emissions. EPA-600/2-77-107e (National Technical Information Service No. PB 270 550), 1977.

2. Suspected Carcinogens - A Subfile of the NIOSH Toxic Substances List, 1976 Edition, H. E. Christensen, ed. Publication No. (NIOSH) 75-188, U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health.

3. Registry of Toxic Effects of Chemical Substances, Volumes I and II, E. J. Fairchild, ed. DHEW Publication No. (NIOSH) 78-104-A, U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, September 1977.

4. Sawicki, E. Chemical Composition and Potential "Genotoxic" Aspects of Polluted Atmospheres. In: Air Pollution and Cancer in Man, U. Mohr, D. Schmahl, and L. Tomatis, eds. International Agency for Research on Cancer Scientific Publication No. 16, 1977. pp. 127-157.

5. Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Volumes 1 through 7. DHEW Publication No. (NIH) 75, Public Health Service Publication No. 149, U.S. Department of Health, Education, and Welfare, National Institutes of Health.

6. Fuller, B., et al. Preliminary Scoring of Selected Organic Air Pollutants. National Technical Information Service Nos. PB 264 442 through PB 264 446, 1976.

7. Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 161, 1975.

8. Radding, S. B., et al. Review of the Environmental Fate of Selected Chemicals. EPA-560/5-77-003 (National Technical Information Service No. PB 267 121), May 1977.

9. Mutation Research, 57:11-15, 1978.

10. Journal of Agricultural and Food Chemistry, 24:560, 1976.

11. Biochemical Pharmacology, 26(8):729-734, 1977.

12. Mutation Research, 31:268-269, 1975.

13. Mutation Research, 40(2):73-83, 1976.

14. Mutation Research, 40(3):273-275, 1976.

15. Cancer Research, 34:2576, 1974.

16. Proceedings of the National Academy of Sciences of the United States, 72(6):2423-2427, 1975.

17. International Agency for Research on Cancer Scientific Publication No. 12, 1976. pp. 61, 125, and 623.

18. International Agency for Research on Cancer Scientific Publication No. 10, 1974. pp. 161-181.

19. Seasonal & Annual (Day/Night) Wind Distribution by Pasquill Stability Classes (6), STAR Program. U.S. Department of Commerce, National Oceanic and Atmospheric Administration, Environmental Data Service, National Climatic Center, Asheville, North Carolina, July 15, 1977.

20. Holzworth, G. C. Estimates of Mean Maximum Mixing Depths in the Contiguous United States. Monthly Weather Review, 92(5):235-242, 1964.

21. Statistical Abstract of the United States, 97th Edition. U.S. Bureau of the Census, Washington, D.C., 1976. p. 191.

22. Khan, Z. S., and T. W. Hughes. Source Assessment: Polyvinyl Chloride. EPA-600/2-78-004i, U.S. Environmental Protection Agency, Cincinnati, Ohio, May 1978. 105 pp.

23. Scientific and Technical Assessment Report on Vinyl Chloride and Polyvinyl Chloride. EPA-600/6-75-004, U.S. Environmental Protection Agency, Washington, D.C., December 1975. 130 pp.

24. Busse, A. D., and J. R. Zimmerman. User's Guide for the Climatological Dispersion Model. EPA-R4-73-024, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, December 1973. 144 pp.

25. Davies, J. C. Co-Carcinogenesis with Respect to the Contents of Cigarette Tobacco. R. Soc. Health J., 93(6):296-301, 1973.

26. Hartwell, J. L. Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Second Edition. National Technical Information Service No. PB 216 478, 1951.

27. Shabad, L. M., et al. The Feasibility of Preventing the Effects of Carcinogens on Man. Kazan Med. Zh, (5):92-93, 1973.

28. Terrell, J. H., and I. Schmeltz. Cigarettes: Chemical Effect of Sodium Nitrate Content. Science, 160:1456, 1968.

29. Izard, C. Mutagenic Effects of Acrolein and its Two Epoxides, Glycidol, and Glycidal, in *Saccharomyces Cerevisiae*. C. R. Acad. Sci., Ser. D., 276(23):3037-3040, 1973.

30. Epstein, S. S., et al. Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse. Toxicol. Appl. Pharmacol., 23:288-325, 1972.

31. Bignami, M., et al. Relationship Between Chemical Structure and Mutagenic Activity in Some Pesticides: The Use of *Salmonella Typhimurium* and *Aspergillus Nidulans*. Mutat. Res., 46(3):243-244, 1977.

32. Allport, J., et al. A Study of Industrial Data on Candidate Chemicals for Testing. National Technical Information Service No. PB 274 264, 1977.

33. Verschueren, K. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Co., New York, 1977.

34. Milvey, P., and M. Wolff. Mutagenic Studies with Acrylonitrile. Mutat. Res., 48(3-4):271-278, 1977.

35. Venitt, S., et al. Mutagenicity of Acrylonitrile (Cyanoethylene) in *Escherichia Coli*. Mutat. Res., 45:283-288, 1977.

36. Acrylonitrile Linked to Cancer in Workers. Chem. Eng. News, 55:6, 1977.

37. Finklea, J. F. Acrylonitrile. Am. Ind. Hyg. Assoc. J., 38:417-422, 1977.

38. Song, J., and W. E. Harville. Carcinogenicity of Aldrin and Dieldrin on Mouse and Rat Liver. Fed. Proc., 23:336, 1964.

39. Diechmann, W. B., et al. Tumorigenicity of Aldrin, Dieldrin, and Endrin in the Albino Rat. Ind. Med. Surg., 39(10): 426-434, 1950.

40. Wurster, C. F. Aldrin and Dieldrin. Environment, 13(8): 33-45, 1971.

41. Epstein, S. S. Prevention - Environmental Exposure: An Overview, Including the Role of Pesticides. Third International Symposium on Detection and Prevention of Cancer, 1976. p. 5.

42. Epstein, S. S. Case Study 5: Aldrin and Dieldrin Suspension Based on Experimental Evidence and Evaluation and Societal Needs. Ann. N.Y. Acad. Sci., 271:187-195, 1976.

43. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 25-38.

44. Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 164, 1975.

45. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 27-36.

46. Fluck, E. R., et al. Evaluation of a DNA Polymerase-Deficient Mutant of *E. Coli* for the Rapid Detection of Carcinogens. Chem. Biol. Interact., 15:219-231, 1976.

47. Schmall, D. Prufung von Naphthalin und Anthracen auf Carcerogene Wirking an Ratten. Zeitschrift fur Krebsforschung, 60:697-710, 1955.

48. Stanton, M. F., et al. J. Natl. Cancer Institute, 49(3): 867-877, 1972.

49. Pienta, R. J., et al. Morophological Transformation of Early Passage Golden Syrian Hamster Embryo Cells Derived from Cryopreserved Primary Cultures as a Reliable *in Vitro* Bioassay for Identifying Diverse Carcinogens. Int. J. Cancer, 19:642-655, 1977.

50. DiPaolo, J. A., et al. Qualtitation of Chemically Induced Neoplastic Transformation of BALB/3T3 Cloned Cell Lines. Cancer Research, 32:2686-2695, 1972.

51. Purchase, I. F. H., et al. Evaluation of Six Short-Term Tests for Detecting Organic Chemical Carcinogens and Recommendations for Their Use. Nature, 264:624-627, 1976.

52. McCann, J., et al. Detection of Carcinogens as Mutagens in the *Salmonella*/Microsome Test, Assay of 300 Chemicals. Proc. Natl. Acad. Sci. (USA), 72:5135-5139, 1975.

53. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3, 1973. pp. 45-68.

54. TLVs® Threshold Limit Values for Chemical Substances and Physical Agents in the Workroon Environment with Intended Changes for 1977. American Conference of Governmental Industrial Hygienists, 1977.

55. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 203-222.

56. Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 162, 1975.

57. Walker, P. Air Pollution Assessment of Benzene. National Technical Information Service No. PB 256 734, 1976.

58. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 80-86.

59. Vesselinovitch, S. D., et al. Factors Modulating Benzidine Carcinogenicity Bioassay. Cancer Res., 35(10):2814-2819, 1975.

60. Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 163, 1975.

61. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3, 1973. pp. 91-136.

62. Takizawa, N. On the Carcinogenic Action of Certain Quinones. Proc. Imperial Acad. (Tokyo), 16:309-312, 1940.

63. Tiedmann, H. Ztschr. Naturforsch., 8b:49-50, 1953.

64. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 1977. pp. 255-264.

65. Vogel, E. Differential Sensitivity of Immature and Mature Oocytes of *Drosophila Melanogaster* to the Induction of Dominant Lethals Following Treatment of Mono- and Polyfunctional Aziridine Analogues. Mutat. Res., 14:250-253, 1972.

66. Lueers, H., and G. Obe. Possible Mutagenic Activity of *p*-Benzoquinone. Mutat. Res., 15:77-80, 1972.

67. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976.

68. McCann, J., et al. Detection of Carcinogens as Mutagens: Bacterial Tester Strains with R Factor Plasmids. Proc. Nat. Acad. Sci (USA), 72:979-983, 1975.

69. Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume I. National Technical Information Service No. PB 223 159, 1968.

70. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 231-238.

71. Smith, A. H., and L. Ellis. Styrene Butadiene Rubber Synthetic Plants and Leukemia (Letter to Editor). J. Occup. Med., 19(7):441, 1977.

72. DiVito, G., and G. L. Sommi. The Incidence of Infectious Diseases, Hemopathies, and Neoplasms in Workers Exposed to Carbon Disulfide. Folia Med. (Napoli), 46(11):972-979, 1963.

73. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 53-60.

74. Johns, R. Air Pollution Assessment of Carbon Tetrachloride. National Technical Information Service No. PB 256 732, 1976.

75. Fishbein, L. Industrial Mutagens and Potential Mutagens, I. Halogenated Aliphatic Derivatives. Mutat. Res., 32:267-308, 1976.

76. Fuhrman, F. A., et al. Arch. Inst. Pharmacodym., 102:113-125, 1955.

77. Innes, J. R. M., et al. J. Nat. Cancer Inst., 42:1101-1114, 1969.

78. Elmore, J. D., et al. Vinyl Chloride Mutagenicity via the Metabolites Chlorooxirane and Chloracetaldehyde Monomer Hydrate. Biochem. Biophys. Acta, 442:409-419, 1976.

79. Rannug, U., et al. The Mutagenicity of Chloroethylene Oxide, Chloroacetaldehyde, 2-Chloroethanol and Chloroacetic Acid, Conceivable Metabolites of Vinyl Chloride. Chem. Biol. Interact., 12(3-4):251-263, 1976.

80. Bartsch, H., et al. Human, Rat and Mouse-Liver Mediated Mutagenicity of Vinyl Chloride in *S. Typhimurium* Strains. Int. J. Cancer, 15(3):429-437, 1975.

81. Malaveille, C., et al. Mutagenicity of Vinyl Chloride, Chloroethyleneoxide, Chloroacetaldehyde and Chloroethanol. Biochem. Biophys. Res. Comm., 63(2):363-370, 1975.

82. Bioassay of Chlordane for Possible Carcinogenicity (CAS No. 57-74-9). National Technical Information Service No. PB 271 977.

83. Bakke, O. M., and T. Midtvedt. Influence of Germ-Free Status on the Excretion of Simple Phenols of Possible Significance in Tumor Promotion. Experimentia, 26(5):519, 1970.

84. Bock, F. G., et al. Composition Studies on Tobacco. XLIV. Tumor-Promoting Activity of Subfractions of the Weak Acid Fraction of Cigarette Smoking Condensate. J. Nat. Cancer Inst., 47(2):429-436, 1971.

85. Shustova, M. N., and L. N. Samiolovich. Blastomogenicity of Neutralized Soots from the Sulfate Shop of a Coke Plant. Gig. Sanit., 36(7):103-104, 1971.

86. Bone, E. S., et al. The Production of Urinary Phenols by Human Gut Bacteria, (Meeting Abstract). J. Med. Microbiol., 9(2):vi, 1976.

87. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 75-81.

88. Jurek, A. Carcinogenicity of Pesticides. Roczn. Panstw. Zakl. Hig., 25(5):563-576, 1974.

89. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 61-65.

90. Powers, M. B., and R. W. Yoelker. Evaluation of the Oncogenic Potential of Chloroform by Long-Term Oral Administration in Rodents (Meeting Abstract). Toxicol. Appl. Pharmacol., 37:179, 1976.

91. Renne, R. A., et al. Pathology of Long-Term Oral Administration of Chloroform in Rodents (Meeting Abstract). Toxocol. Appl. Pharmacol., 37:179-180, 1976.

92. Chloroform Tagged as Carcinogen in Mice. Chem. Eng. News, 54:6, 1976.

93. Khachatryan, E. A. The Role of Chloroprene in the Process of Skin Neoplasm Formation. Gig. Tr. Prof. Zabol., 16:54-55, 1972.

94. Khachatryan, E. A. The Occurrence of Lung Cancer Among People Working with Chloroprene. Problems in Oncology, 18:85, 1972.

95. Khachatryan, E. A. Lung Cancer Incidence Among Chloroprene Handling Workers. Yopr. Onkol., 18:85-86, 1972.

96. Casto, B. C., et al. Assay of Industrial Chemicals in Syrian Hamster Cells for Enhancement of Viral Transformation. Proc. Am. Assoc. Cancer Res., 18:155, 1977.

97. Bartsch, H., et al. The Predictive Value of Tissues-Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals. IARC Sci. Pub. No. 12, 1976. pp. 467-491.

98. Zilfyan, V. N., et al. Experimental Study of Chloroprene for Carcinogenicity. Yopr. Onkol., 23:61-65, 1977.

99. Zilfyan, V. N., et al. Results of a Study of Chloroprene for Carcinogenicity. Zh. Eksp. Klin. Med., 15:54-57, 1975.

100. Lloyd, J. W. Cancer Risks Among Workers Exposed to Chloroprene. Ann. N.Y. Acad. Sci., 271:91-93, 1976.

101. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3, 1973. pp. 159-177.

102. Epstein, S. S., and H. Shafner. Chemical Mutagens in the Human Environment. Nature, 219:385-387, 1963.

103. Radiation Research, Supplement 3:193, 1963 (as cited in Reference 2).

104. J. Nat. Cancer Inst., 37:825, 1966 (as cited in Reference 2).

105. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 83-124.

106. Vogel, E. The Relation Between Mutational Pattern and Concentration by Chemical Mutagens in *Drosophila*. IARC Sci. Pub. No. 12, 1976. pp. 117-137.

107. Kotin, P., and H. L. Falk. Radiation Research Supplement 3:193-211, 1963 (as cited in Reference 5).

108. Saffioti, U., and P. Shubik. Nat. Cancer Inst. Monog., 10:489-507, 1963 (as cited in Reference 5).

109. Hoshing, H., et al. Gann 61(2):121-124, 1970 (as cited in Reference 5).

110. Van Duuren, B. L., et al. J. Nat. Cancer Inst., 39:1217-1228, 1967 (as cited in Reference 5).

111. Documentation of the Threshold Limit Values for Substances in Workroom Air. American Conference of Governmental Industrial Hygienists, 1976. pp. 96-97.

112. Shubik, P., et al. Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Supplement I. National Technical Information Service No. PB 216 248, 1957.

113. Singh, A. R., et al. Mutagenic and Antifertility Sensitivities of Mice to Di-2-ethylhexyl Phthalate (DEHP) and Dimethoxyethyl Phthalate (DMEP). Toxicol. Appl. Pharmacol., 29(1):35-46, 1974.

114. Mathur, S. P. Respirometric Evidence of the Utilization of Dioctyl and Di-2-ethylhexyl Phthalate Plasticizers. J. Environ. Qual., 3(3):207-209, 1974.

115. Peakall, D. B. Phthalate Esters: Occurrence and Biological Effects. Residue Reviews, 54:1-41, 1975 (177 references).

116. Recent Progress in Safety Evaluation Studies on Plasticizers and Plastics and Their Controlled Use in Japan. Environ. Health Perspec., 17:203-209, 1976.

117. Singh, A. R., et al. Mutagenic and Antifertility Sensitivities of Mice to Phthalic-Acid Esters. J. Anim. Sci., 38(1):216, 1974.

118. Taylor, B. F., and E. F. Corcoran. Biodegradation of Phthalic Acids and Esters. Contract ES-00994-02, National Institute of Environmental Health Sciences, 1975.

119. Autain, J. Toxicity and Health Threats of Phthalate Esters, Review of the Literature. Environ. Health Perspec., 4:3-26, 1973.

120. Yagi, Y., et al. Teratogenicity and Mutagenicity of a Phthalate Ester. Teratology, 14:259-260, 1976.

121. Dillingham, E. O., and J. Autain. Teratogenicity, Mutagenicity and Cellular Toxicity of Phthalate Esters. Environ. Health Perspec. 3:81-89, 1973.

122. Landon, J. C. Carcinogenesis Bioassay of Di(2-ethylhexyl) Phthalate. National Cancer Institute contract with Tracor Jitco, Inc., 10/76-9/77, 1977.

123. Saeger, V. W., and E. S. Tucker. Biodegradation of Phthalic Acid Esters in River Water and Activated Sludges. Appl. Environ. Microbiol., 31(1):29-34, 1976.

124. Palmer, K. A., et al. The Mutagenic Assay of Some Hair Dye Components Using the Thymidine Kinane Locus of L51178Y Mouse Lymphoma Cells (Meeting Abstract). Toxicol. Appl. Pharmacol., 37(1):108, 1976.

125. Kinkel, H. J., and S. Holzmann. Study of Long-Term Percutaneous Toxicity and Carcinogenicity of Hair Dyes (Oxidizing Dyes) in Rats. Food Cosmet. Toxicol., 11(4):641-648, 1973.

126. Burnett, C., et al. Long-Term Toxicity Studies on Oxidation Hair Dyes. Food Cosmet. Toxicol., 13(3):353-357, 1975.

127. Burnett, C., et al. Dominant Lethal Mutagenicity Study on Hair Dyes. J. Toxicol. Environ. Health, 2(3):657-662, 1977.

128. Dybing, E., and S. S. Thorgeirsson. Metabolic Activation of 2,3-Diaminoanisole, a Hair-Dye Component. Biochem. Pharmacol., 26(8):729-734, 1977.

129. Dybing, E., and T. Aune. Hexachlorobenzene Induction of 2,4-Diaminanisole Mutagenicity *in Vitro*. Acta Pharmacol. Toxicol., 40(5):575-583, 1977 (24 references).

130. Ames. B. N., et al. Hair Dyes are Mutagenic; Identification of a Variety of Mutagenic Ingredients. Proc. Natl. Acad. Sci. (USA) 72(6):2423-2427, 1975.

131. Blijleven, W. G. Mutagenicity of Four Hair Dyes in *Drosphila Melanogaster*. Mutat. Res., 48(2):181-185, 1977.

132. Health Hazards; 2,4-Diaminoanisole. Occupational Safety & Health Reporter, 7(35):1331, 1978.

133. 2,4-Diaminoanisole (4-Methoxy-*m*-phenylenediamine) in Hair and Fur Dyes. Current Intelligence Bulletin 19, January 13, 1978.

134. Kimbrough, R. D., and T. B. Gaines. Effect of Organic Phosphorous Compounds and Alkylating Agents on the Rat Fetus. Arch. Environ. Health, 16:805-808, 1968.

135. Trinh-Van-Bao, et al. Chromosome Aberrations in Patients Suffering Acute Organic Phosphate Insecticide Intoxication. Humangenetik, 24:33-57, 1974.

136. Tzoneva-Maneva, M. T., et al. Influence of Diazinon and Lindane on the Mitotic Activity and the Caryotype of Human Lymphocytes, Cultivated *in Vitro*. Bibl. Haematol. (Base 1), 38(1):344-347, 1971.

137. Marshall, T. C., et al. Screening of Pesticides for Mutagenic Potential Using *Salmonella Typhimurium* Mutants. J. Agric. Food Chem., 24:560-563, 1976.

138. Mohn, G. 5-Methyltryptophan Resistance Mutations in *Escherichia Coli* K-12. Mutat. Res., 20(1):7-15, 1973.

139. Ashwood-Smith, M. J., et al. Mutagenicity of Dichlorvos. Nature, 240:418-419, 1972.

140. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 231-244.

141. Guerin, M., et al. Inhibitory Action of Chemical Carcinogens on Mitosis of Rat Lung Cell Cultures; 2. Comparative Study of Carcinogenic and Noncarcinogenic Substances. C. R. Soc. Biol., 165:2255-2258, 1971.

142. Prasad, I. Mutagenic Effects of the Herbicide 3',4'-Dichloro-propionanilide and Its Degradation Products. Can. J. Microbiol., 16:369-372, 1970.

143. Prasad, I., and D. Pramer. Mutagenic Activity of Some Chloroanilines and Chlorobenzenes. Genetics, 60:212-213, 1968.

144. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 49-55.

145. Stula, E. F., et al. Experimental Neoplasia in Rats from Oral Administration of 3,3-Dichlorobenzidine, 4,4'-Methylenebis(2-chloroaniline), and 4,4'-Methylenebis(2-methylaniline). Toxicol. Appl. Pharmacol., 31(1):159-176, 1975.

146. Bartsch, H., et al. Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissues. Proc. Am. Assoc. Cancer Res., 17:17, 1976.

147. Van Duuren, B. L., et al. Carcinogenic Activity of Di- and Tri-functional α-Chloro Ethers and of 1,4-Dichlorobutene-2 in ICR/HA Swiss Mice. Cancer Res., 35:2553-2557, 1975.

148. Andrews, A. W., et al. The Identification of Endogeneous and Exogeneous Mutagenic Compounds. 4th Carcinogenesis Bioassay Program, Orlando, Florida, February 1976.

149. Stevens, S., et al. Phenotypic and Genetic Effects in *Neurospora Crassa* Produced by Selected Gases and Gases Mixed with Oxygen. Develop. Ind. Microbiol., 12:346-353, 1971.

150. Schwetz, B. A., et al. Embryo- and Fetotoxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane, and Methyl Ethyl Ketone in Rats. Toxicol. Appl. Pharmacol., 28:452-464, 1974.

151. National Cancer Institute Draft Summaries of Bioassay Reports, 1,1-Dichloroethane. Chem. Reg. Rep., 1(45):1597-1598, 1978.

152. Anderson, K. J., et al. Evaluation of Herbicides for Possible Mutagenic Properties. J. Agr. Food Chem., 20:649-656, 1972.

153. Boutwell, R. K., and D. K. Bosch. The Tumor-Promoting Action of Phenol and Related Compounds for Mouse Skin. Cancer Res., 19:413-424, 1959.

154. Torkelson, T. R., and F. Oyen. The Toxicity of 1,3-Dichloropropene as Determined by Repeated Exposure of Laboratory Animals. Am. Indust. Hyg. Assoc. J., 38(5):217, 1977.

155. DeLorenzo, F., et al. Mutagenicity of Pesticides Containing 1,3-Dichloropropene. Cancer Res., 37(6):1915-1917, 1977.

156. Neudecher, T., et al. *In Vitro* Mutagenicity of the Soil Nematicide 1,3-Dichloropropene. Experientia, 33(8):1084-1085, 1977.

157. Shirasu, Y., et al. Mutagenicity Screening of Pesticides in the Microbial System. Mutat. Res., 40:19-30, 1976.

158. Bioassay of Dichlorvos for Possible Carcinogenicity, CAS No. 62-73-7. National Technical Information Service No. PB 270 937, 1977.

159. Rieger, M. M. Cosmetic Science: 1975 Literature Survey. Cosmet. Perfum., 91(4):25-36, 1976.

160. Hadidian, Z., et al. J. Nat. Cancer Inst., 41(4):985-1036, 1968.

161. Dushutin, K. K., and E. D. Sopach. The Role of the Reaction of Dimethylamine with Nitrogen Tetroxide and Ozone in Atmospheric Pollution. Gig. Sanit., 7:14-18, 1976.

162. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 137-143.

163. Wilson, R. B. Species Variation in Response to Dimethylhydrazine. Toxicol. Appl. Pharmacol., 38(3):647-650, 1976.

164. National Cancer Institute Draft Summaries of Bioassay Reports, 2,4-Dinitrotoluene. Chem. Reg. Rep., 1(45):1598, 1978.

165. Kociba, R. J., et al. 1,4-Dioxane: Correlation of the Results of Chronic Ingestion and Inhalation Studies with its Dose-Dependent Fate in Rats. Aerosp. Med. Res. Lab. (Tech. Rep.) AMRL-TR-125, 1975. pp. 345-354.

166. Argus, M. F., et al. Dose-Response and Ultrastructural Alternatives in Dioxane Carcinogenesis. Eur. J. Cancer, 9(4):237-243, 1973.

167. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 247-256.

168. Torkelson, T. R., et al. 1,4-Dioxane. II. 2-Year Inhalation Study in Rates. Toxicol. Appl. Pharmacol., 30(2): 287-298, 1974.

169. Simmon, V. F., et al. *In Vitro* Mutagenic Studies of Twenty Pesticides. Toxicol. Appl. Pharmacol., 37(1):109, 1976.

170. National Cancer Institute Draft Summaries of Bioassay Reports. Chem. Reg. Rep., 1(45):1608-1609, 1978.

171. Grant, W. F. Cytological Effects of Environmental Mutagens-Pesticides. Mutat. Res., 21(4):221-222, 1973.

172. Van Dijck, P., and H. Van de Voorde. Mutagenicity Versus Carcinogenicity of Organochloride Insecticides. Meded. Fac. Landbouwwet., Rijksuniv. Gent, 41(2, part 2):1491-1498, 1976.

173. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 157-171.

174. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 131-139.

175. Kurinnyi, A. I. Mutagenic Activity of Some Pesticides Derivatives of Urea, Carbamic, and Thiocarbamic Acids. Tsitol. Genet., 11(4):357-359, 1977.

176. Hakeek, H., and A. Shehab. Cytological Effects of Eptam and Cotoran on *Vicia Faba*. Egypt. J. Bot., 16(1-3):303-311, 1974.

177. Rydberg, U., and S. Skerfuing. The Toxicity of Ethanol: A Tentative Risk Evaluation. Adv. Exp. Med. Biol., 85B: 403-419, 1977 (57 references).

178. Braun, R., and J. Schoeneick. Influences of Ethanol and Carbon Tetrachloride on the Mutagenic Effectivity of Cyclophosphamide in the Host-Mediated Assay with *Salmonella Typhimurium*. Mutat. Res., 31(3):191-194, 1975.

179. Charbey, R. C., et al. Evaluation of the Effect of Ethanol on the Frequency of Micronuclei in the Bone Marrow of Swiss Mice. Mutat. Res., 43(3):441-444, 1977.

180. Opdyke, D. L. Monographs on Fragrance Raw Materials Ethylbenzene. Food Cosmet. Toxicol., 13(Suppl.):803-804, 1975.

181. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 1977. pp. 195-209.

182. Johns, R. Air Pollution Assessment of Ethylene Dibromide. National Technical Information Service No. PB 256 736, 1976.

183. New Findings on Two Carcinogens Reported to Subcommittee by NIOSH. Occupational Safety & Health Reporter, 7(35):1331, 1978.

184. Johns, R. Air Pollution Assessment of Ethylene Dichloride. National Technical Information Service No. PB 256 733, 1976.

185. Homburger, F. Carcinogenicity of Several Compounds. National Technical Information Service No. PB 183 027, 1968. 26 pp.

186. Mason, M. M. Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines. National Technical Information Service No. PB 195 185, 1969. 55 pp.

187. Derse, P. H. Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety. National Technical Information Service No. PB 195 153, 1969. 135 pp.

188. Coon, R., et al. Animal Inhalation Studies on Ammonia, Ethylene Glycol, Formaldehyde, Dimethylamine, and Ethanol. Toxicol. Appl. Pharmacol., 16(3):645-646, 1970.

189. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 157-167.

190. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 9, 1976. pp. 37-46.

191. Arcos, J. C., and M. F. Argus. Chemical Induction of Cancer, Volume 11A. Academic Press, New York, 1974. pp. 26, 237.

192. Hoffman, D., et al. J. Natl. Cancer Inst., 49:1165-1175, 1972.

193. Rao, T. K., et al. Environmental Mutagenesis of Energy-Related Effluents. Genetics, 83:S60, 1976.

194. Watanabe, F., et al. Gann, 45:451-452, 1954 (as cited in Reference 5).

195. Investigation of Selected Potential Environmental Contaminants: Formaldehyde. National Technical Information Service No. PB 256 839, 1976.

196. Alam, M. T., and S. S. Kasatiya. Cytological Effects of an Organic Phosphate Pesticide on Human Cells *in Vitro*. Can. J. Genet. Cytol., 18(4):665-671, 1976.

197. Jorgenson, T. A., et al. *In Vivo* Mutagenesis Investigations of Ten Commercial Pesticides. Toxicol. Appl. Pharmacol., 37(1):109, 1976.

198. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 173-191.

199. Bioassay of Heptachlor for Possible Carcinogenicity, CAS No. 76-55-8. National Technical Information Service No. PB 271 967.

200. Khera, K. S. Hexachlorobenzene: Teratogenicity and Dominant Lethal Studies in Rats. Toxicol. Appl. Pharmacol., 29(1):109, 1974.

201. Boyland, E., et al. Kidney Tumors in Rats Following Treatment with 2-Acetylaminofluorene, Tryptophan, and 14-Saccharolactone and the Failure of Substances Which Cause Porphyrinuria to Induce Tumors. In: British Empire Cancer Campaign 1963 - Part 2: Scientific Report, 1963. pp. 58-59.

202. Guerzoni, M. E., et al. Mutagenic Activity of Pesticides. Riv. Sci. Tecnol. Alimenti Nutr. Um. (Ital.), 6(3):161-165, 1976.

203. Cabral, J. R. P., et al. Carcinogenic Activity of Hexachlorobenzene in Hamsters. Nature, 269(5628):510-511, 1977.

204. Test for Carcinogenicity of Organic Contaminants of United States Drinking Waters by Pulmonary Tumor Response in a Strain of Mice. Cancer Res., 37(8):2717-2720, 1977.

205. Results of a Two-year Chronic Toxicity Study with Hexachlorobutadiene in Rats (Meeting Abstract). Toxicol. Appl. Pharmacol., 41(1):204, 1977.

206. Kociba, R. J., et al. Results of a Two-Year Chronic Toxicity Study with Hexachlorobutadiene in Rats. Am. Ind. Hyd. Assoc. J., 38(11):589-602, 1977.

207. Reproduction Study in Japanese Quail Fed Hexachlorobutadiene for 90 days. Toxicol. Appl. Pharmacol., 30(2):255-265, 1974.

208. Della Porta, G., et al. Non-Carcinogenicity of Hexamethylenetetramine in Mice and Rats. Food Cosmet. Toxicol., 6(6):707-715, 1968.

209. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 127-136.

210. Roe, F. J. C., and M. H. Salaman. Further Studies on Incomplete Carcinogenesis. British J. of Cancer, 9:177-203, 1955.

211. Boyland, E., et al. Further Experiments on Implantation of Materials into the Urinary Bladder of Mice. British J. of Cancer, 18:575-581, 1964.

212. Van Duuren, B. L., and B. M. Goldschmidt. Cocarcinogenic and Tumor-Promoting Agents in Tobacco. J. Natl. Cancer Inst., 56:1237-1242, 1976.

213. Hecht, S. S., et al. Study of Tobacco Carcinogenesis; XIII: Tumor-Promoting Subfractions of the Weakly Acidic Fraction. J. Natl. Cancer Inst., 55(6):1329-1336, 1975.

214. Interaction Between Hydroquinone and Cigarette Smoke Condensate in Short-Term Skin Tests for Carcinogenicity. TOXLINE.

215. National Cancer Institute Draft Summaries of Bioassay Reports. Chem. Reg. Rep., 1(45):1602-1603, 1978.

216. Silinskas, K. C., and A. B. Okey. Protection by DDT Against Mammary Tumors and Leukemia During Prolonged Feeding of 7,12-Dimethylbenz(a)anthracene to Female Rats. J. Natl. Cancer Inst., 55(3):653-658, 1975.

217. Dickens, F., and H. E. H. Jones. Further Studies on the Carcinogenic and Growth-Inhibitory Activity of Lactones and Related Substances. Brit. J. Cancer, 17:100-108, 1963.

218. Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume III. National Technical Information Service No. PB 223 161, 1968.

219. Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume II. National Technical Information Service No. PB 223 160, 1968.

220. Ehrenberg, L., et al. On the Reaction Kinetics and Mutagenic Activity of Methylating and Beta-Halogenoethylating Gasoline Additives. Radiat. Bot., 14(3):185-194, 1974.

221. Embryo Toxicity and Feto Toxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane, and Methyl Ethyl Ketone in Rats. Toxicol. Appl. Pharmacol., 29(1):123, 1974.

222. Nakahara, W., and K. Mori. Proc. Imp. Acad., Japan, 15:278-281, 1939 (as cited in Reference 5).

223. Nakahara, W., and K. Mori. Gann, 34:143-145, 1940 (as cited in Reference 5).

224. Horton, A. W., et al. Cancer Research, 25:1759-1763, 1965 (as cited in Reference 5).

225. Singh, A. R., et al. Embryonic-Fetal Toxicity and Teratogenic Effects of a Group of Methacrylate Esters in Rats. J. Dental Research, 51:1632-1638, 1972.

226. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 65-71.

227. OSHA Compliance Guide, 29 CFR Part 1910, 1978.

228. Methylene Chloride Passes Early Tests. Chem. Eng. News, 55(19):6, 1977.

229. Mutation Research, Volume 53, January 1978.

230. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 79-85.

231. Schoental, R. Carcinogenic and Chronic Effects of 4,4'-Diaminodiphenylmethane, an Epoxyresin Hardener. Nature, 219:1162-1163, 1968.

232. Steinhoff, D., and E. Grundmann. Zur Cancerogenen Wirkung von 4,4'-Diaminodiphenylmethan und 2,4'-Diaminodiphenylmethan. Naturioissenschaften, 57:247-248, 1970.

233. Gigiena i Sanitariya, 34:40, 1969. (Translated in Hygiene and Sanitation.)

234. Toxic Substances: Proposed Occupational Safety and Health Standards for Alkyl Benzenes, Cyclohexane, Ketones, and Ozone. Fed. Regist. 40(196):47262-47313, 1975.

235. Effect of Alpha-Methylstyrene and Tert-Dodecyl Mercaptan on the Skin of Animals. Vop. Gig. Tr. Profzabol., Mater. Nauch. Konf.; 1972. pp. 247-249.

236. Reversible Damage to the Skin of Experimental Animals Subjected to the Inhalation of Butadiene and Alpha-Methylstyrene. Mater. Nauch. Sess., Posoyashck. 50-Letiyu Obrazov. SSSR, Omsk. Gas. Med. Inst.; 1972. pp. 871-873.

237. Effect of Isopropylbenzene and Alpha-Methylstyrene on Leucopoiesis. Farmakol. Toksikol., 35(4):491-492, 1972.

238. Effect of the Wastes from Phenol Production on Housefly Larvas. Mater. Konf. Molodykh. Uch. Stud., Posvyashch. 50-Letiyu SSSR; 1973. pp. 375-377.

239. Greenblat[illegible], M., et al. J. Natl. Cancer Inst., 46(5):1029-1034, 1971 (as cited in Reference 5).

240. Sander, J., and G. Bunkle. Z. Krebsforsch, 73(1):54-66, 1969.

241. Fomenko, V. N., and E. E. Strekalova. Mutagenic Action of Some Industrial Poisons as a Function of Concentration and Exposure Time. Toksikol. Nov. Prom. Khim. Veshehestv., 13:51-57, 1973 (CA 79:143228).

242. Migukina, N. V. Evaluation of the Danger of Morpholine During Chronic Action. Toksikol. Nov. Prom. Khim. Veshehestv., 13:92-100, 1973 (CA 79:143345).

243. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 87-96.

244. OSHA Compliance Guide, 29 CFR Part 1910, 1004, 1978. pp. 298-300.

245. Arcos, J. C., and M. F. Argus. Chemical Induction of Cancer, Volume IIA. Academic Press, New York, 1974. pp. 194, 237, and 278.

246. Kraemer, M., et al. *S. Typhimurium* and *E. Coli* to Detect Chemical Mutagens. Naunyn-Schmiedebergs Arch. Pharmakol., 284:46R, 1974.

247. Zabezhinskiy, M. A. Investigations on Possible Carcinogenic Effects of Beta-Sevin. Vopr. Onkol., 16(11):106-107, 1970.

248. Dorigan, J., and J. Hushon. Air Pollution Assessment of Nitrobenzene. National Technical Information Service No. PB 257 776, May 1976.

249. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 95-106.

250. Bretschneider, K., and J. Matz. Occurrence and Analysis of Nitrosamines in Air. IARC Sci. Pub. No. 14, 1976. pp. 395-399.

251. Fine, D. H., et al. N-Nitroso Compounds in Air and Water. IARC Sci. Pub. No. 14, 1976. pp. 401-408.

252. Tradiff, R. G., et al. Halogenated Organics in Tap Water: A Toxicological Evaluation. In: The Environmental Impact of Water Chlorination, National Technical Information Service No. CONF 751096, 1976. pp. 213-228.

253. Vogel, E., and J. L. R. Chandler. Mutagenicity Testing of Cyclamate and Some Pesticides in *Drosophila Melanogaster*. Experientia, 30(6):621-623, 1974.

254. Buselmaier, W., et al. Comparative Investigations on the Mutagenicity of Pesticides in Mammalian Test Systems. Mutat. Res., 21(1):25-26, 1973.

255. Daugherty, R. C., and K. Piotrowska. Screening by Negative Chemical Ionization Mass Spectrometry for Environmental Contamination with Toxic Residues: Application to Human Urines. Proc. Natl. Acad. Sci., 73(6):1777-1781, 1976.

256. Salaman, M. H., and O. M. Glendenning. Brit. J. Cancer, 11:434-444, 1957.

257. Hossak, D. J., and J. C. Richardson. Examination of the Potential Mutagenicity of Hair Dye Constituents Using the Micronucleus Test. Experientia, 33(3):377-378, 1977.

258. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 261-289.

259. Lloyd, J. W., et al. Polychlorinated Biphenyls. J. Occup. Med., 18(2):109-113, 1976.

260. Andrews, E. J., et al. PCB Diet. Science, 180(4083):255-257, 1973.

261. Ito, N., et al. Histopathological Studies on Liver Tumorigenesis in Rats Treated with Polychlorinated Biphenyls. Gann, 65(6):545-549, 1974.

262. Lawrence, C. PCB? and Melanoma (letter to the editor). N. Engl. J. Med., 296(2):108-109, 1977.

263. Gibel, W., et al. Experimental Study on Cancerogenic Activity of Propanol-1, 2-Methylpropanol-1, and 3-Methylbutanol. Arch. Geschwulstforsch, 45(1):19-24, 1975.

264. Gibel, W., et al. Studies on the Toxicity and Mutagenicity of Single Fusel Oil Components on *E. Coli*. Acta Biol. Med. Ger., 23:843-852, 1969.

265. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 1977. pp. 223-243.

266. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 191-199.

267. Rowe, L. K., et al. Toxicity of Propylene Oxide Determined on Experimental Animals. Arch. Industr. Hlth., 13:228-236, 1956.

268. Arcos, J. C., and M. F. Argus. Chemical Induction of Cancer, Volume IIA, Academic Press, New York, 1974. pp. 210, 237.

269. Dickens, F., et al. Brit. J. Cancer, 20:134-144, 1966.

270. Dickens, F., and H. B. Wayforth. Brit. Emp. Canc. Camp., 46:108, 1968.

271. Dickens, F., et al. Brit. J. Cancer, 22:762-768, 1968.

272. Grant, I. F., et al. Long-Term Toxicity of Sorbic Acid in the Rat. Food Cosmet. Toxicol., 13(1):31-45, 1975.

273. Hendy, R. J., et al. Long-Term Toxicity Studies of Sorbic Acid in Mice. Food Cosmet. Toxicol., 14(5):381-386, 1976.

274. Mason, P. L., et al. Long-Term Toxicity of Parasorbic Acid in Rats. Food Cosmet. Toxicol., 14(5):387-394, 1976.

275. Kada, T. Mutagenicity and Carcinogenicity Screening of Food Additives by the Rec-Assay and Reversion Procedures. IARC Sci. Pub. No. 12, 1976. pp. 105-115.

276. DeMeester, C., et al. Mutagenic Activity of Styrene and Styrene Oxide. Arch. Int. Physiol. Biochim., 85(2):398-399, 1977.

277. Vainio, H., et al. A Study on the Mutagenic Activity of Styrene and Styrene Oxide. Scand. J. Work Environ. Health, 2(3):147-151, 1976.

278. Stolz, D. R. Mutagenicity Testing of Styrene and Styrene Epoxide in *Salmonella Typhimurium*. Bull. Environ. Contam. Toxicol., 17(6):739-742, 1977.

279. Loprieno, N., et al. Mutagenicity of Industrial Compounds: Styrene and Its Possible Metabolite Styrene Oxide. Mutat. Res., 40(4):317-324, 1976.

280. Yeung, C. K. K., and C. R. Phillips. Estimation of Physiological Smog Sympton Potential from Chemical Reactivity of Hydrocarbons. Atm. Environ., 7, 1973.

281. Gray, A. W. A. Arch. Ind. Hyg., 2:407-419, 1950.

282. Brem, H., et al. The Mutagenicity and DNA-Modifying Effect of Haloalkanes. Cancer Res., 34:2576-2579, 1974.

283. Rosenkranz, H. S. Mutagenicity and DNA-Modifying Activity: A Comparison of Two Microbial Assays. Mutat. Res., 41(1): 61-70, 1976.

284. Kraybill, H. F. Origin, Classification, and Distribution of Chemicals in Drinking Water with an Assessment of their Carcinogenic Potential. In: The Environmental Impact of Water Chlorination, National Technical Information Service No. CONF 751096, 1976. p. 229.

285. Chemical Regulation Reporter, 1(51):1861, 1978.

286. Fuller, B. B. Air Pollution Assessment of Tetrachloroethylene. National Technical Information Service No. PB 256 731, 1976. 99 pp.

287. Bioassay of Tetrachloroethylene for Possible Carcinogenicity, CAS No. 127-18-4. National Technical Information Service No. PB 272 940, 1977.

288. Epstein, S. S., and N. Mantel. Carcinogenicity of Tetraethyl Lead. Experientia, 24(6):580-581, 1968.

289. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 2, 1973. pp. 150-160.

290. Kennedy, G. L., et al. Teratogenic Evaluation of Lead Compounds in Mice and Rats. Food Cosmet. Toxicol., 3(6):629-632, 1975.

291. Robinson, T. R. Health, How Can It Be Measured. In: HEW Publ. (NIOSH) 76-134, 1976. pp. 114-130.

292. Walker, P. Air Pollution Assessment of Toluene. National Technical Information Service No. PB 256 735, 1976.

293. Giles, A. L., et al. Dermal Carcinogenicity Study by Mouse-Skin Painting with 2,4-Toluenediamine Alone or in Representative Hair Dye Formulations. J. Toxicol. Environ. Health, 1(3):433-440, 1976.

294. Bridges, B. A., and M. H. Green. Carcinogenicity of Hair Dyes by Skin Painting in Mice (letter to editor). J. Toxicol. Environ. Health, 2(1):251-252, 1976.

295. Shah, M. J., et al. Comparative Studies of Bacterial Mutation and Hamster Cell Transformation Induced by 2,4-Toluenediamine (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:22, 1977.

296. Cancer Research, 29:1137, 1969.

297. Pienta, R. J., et al. Correlation of Bacterial Mutagenicity and Hamster Cell Transformations with Tumorigenicity Induced by 2,4-Toluenediamine. Cancer Lett. (Amsterdam), 3(1/2): 45-52, 1977.

298. Bioassay of 1,1,1-Trichloroethane for Possible Carcinogenicity. Carcinog. Tech. Rep. Serv. - Nat'l. Cancer Inst. (U.S.); ISS NCI-CG-TR-3, 1975. 70 pp.

299. Carcinogenesis Bioassay of Trichloroethylene, CAS No. 79-01-6. National Cancer Institute Carcinogenesis Technical Report Services, Number 2, February 1976 (NCI-CG-TR-2).

300. Fuller, B. B. Air Pollution Assessment of Trichloroethylene. National Technical Information Service No. PB 256 730, 1976.

301. Epstein, S. S., et al. Synergistic Toxicity and Carcinogenicity of "Freons" and Piperonyl Butoxide. Nature, 214: 526-528, 1967.

302. Uehleke, H., et al. Metabolic Activation of Haloalkanas and Tests *in Vitro* for Mutagenicity. Xenobiotica, 7(7): 393-400, 1977.

303. NCI Preliminary data on trichlorofluoromethane, Nov. 27, 1976.

304. Cytological Effects of Pesticides. V. Effects of Some Herbicides on *Vicia Faba*. Cytologia, 39(4):663-643, 1974.

305. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 111-140.

306. Garibyan, D. K., and S. A. Papoyan. Study of the Blastomogenic Activity of Certain Chemical Substances Using a High-Speed Test Method. Gig. Sanit., 8:74-76, 1977.

307. Garibyan, D. K., and S. A. Papoyan. Use of Sebaceous Gland Reactions as a Test for Rapid Determination of Carcinogenic Activity of Chemicals. Nekot. Itogi Izuch. Zagryazneniya Vnesh. Sredy Kanstserogen. Veschestoami; 112-115, 1972.

308. Barbin, A., et al. Liver-Microsome-Mediated Formation of Alkylating Agents from Vinyl Bromide and Vinyl Chloride. Biochem. Biophys. Res. Comm., 67(2):596-603, 1975.

309. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 291-305.

310. IARC Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity. International Agency for Research on Cancer, Lyon, Bulletin No. 5, July 1975.

311. Greim, H. G., et al. Mutagenicity *in Vitro* and Potential Carcinogenicity of Chlorinated Ethylenes as a Function of Metabolic Oxirane Formation. Biochem. Pharmacol., 24:2013-2017, 1975.

312. Food Additives, Packaging Material for Use During Irradiation of Pre-Packaged Foods. Fed. Register, 33:4569, 1968.

313. Caputo, A., et al. Oncogenicity of Vinyl Chloride at Low Concentrations in Rats and Rabbits. IRCS, 2:1582, 1974.

314. Hushon, J., and M. Kornreich. Air Pollution Assessment of Vinylidene Chloride. National Technical Information Service No. PB 256 738, 1976.

315. Pound, A. W. Induced Cell Proliferation and the Initiation of Skin Tumor Formation in Mice by Ultraviolet Light. Pathology, 2(4):269-275, 1970.

316. Listgarten, M. A., et al. Ultrastructural Alterations in Hamster Cheek Pouch Epithelium in Response to a Carcinogen. Arch. Oral Biol., 8(2):145-165, 1963.

317. Hecker, E. Definitions and Terminology in Carcinogenesis - Analyses and Proposals (Meeting Abstract). Third International Symposium on Detection and Prevention of Cancer, 1976. p. 67.

318. Yuspa, S. H., et al. Cutaneous Chemical Carcinogenesis: Past, Present, and Future. J. Invest. Dermatol., 67(1): 199-208, 1976.

319. Rogers, A. E. Reduction of n-Nitrosodiethylamine Carcinogenesis in Rats by Lipotrope or Amino Acid Supplementation of a Marginally Deficient Diet. Cancer Res., 37(1):194-199, 1977.

320. Syrotuck, J. A., and B. S. Worthington. Nutritional Effects on Syngeneic Tumor Immunity and Carcinogenesis in Mice, I. Selected Essential Amino Acids (Meeting Abstract). Fed. Proc., 36(3):1163, 1977.

321. Leuchtenberger, C., and R. Leuchtenberger. Protection of Hamster Lung Cultures by L-Cysteine Against Carcinogenic Effects of Fresh Smoke from Tobacco or Marihauana Cigarettes (Meeting Abstract). J. Cell. Biol., 70(2/Part 2): 44a, 1976.

322. Takamiua, K., et al. Effect of Phenobarbital and DL-Ethionine on 4-(Dimethylamino)azobenzene-Metabolizing Enzymes and Carcinogenesis. Gann, 64(4):363-372, 1973.

323. Ito, N., et al. The Development of Carcinoma in Liver of Rats Treated with *m*-Toluylenediamine and the Synergistic and Antagonistic Effects with Other Chemicals. Cancer Res., 29(5):1137-1145, 1969.

324. Radomski, J. L., et al. Cocarcinogenic Interaction Between D,L-Tryptophan and 4-Aminobiphenyl or 2-Naphthylamine in Dogs. J. Natl. Cancer Inst., 58(6):1831-1834, 1977.

325. Ito, N., et al. Effect of Various Carcinogenic and Non-carcinogenic Substances on Development of Bladder Tumors in Rats Induced by n-Butyl-N-(4-hydroxybutyl)nitrosoamine. Gann, 65(2):123-130, 1974.

326. Matsushima, M. The Role of the Promoter L-Tryptophan on Tumorigenesis in the Urinary Bladder. 2. Urinary Bladder Carcinogenicity of Fanft (Initiating Factor) and L-Tryptophan (Promoting Factor) in Mice. Jpn. J. Urol., 68(8):731-736, 1977.

327. Rogers, A. E., and P. M. Newberne. Dietary Effects on Chemical Carcinogenesis in Animal Models for Colon and Liver Tumors. Cancer Res., 35(11/Part 2):3427-3431, 1975.

328. Bjelke, E. Dietary Vitamin A and Human Lung Cancer. Int. J. Cancer, 15(4):561-565, 1975.

329. Prutkin, L. Inhibition of Tumorigenesis by Topical Application of Low Doses of Vitamin A Acid and Fluorouracil. Experientia, 31(4):494, 1975.

330. Sugimura, T. Carcinogens in Foods and Food Products. Proceedings of the Eleventh Canadian Cancer Research Conference, Natl. Cancer Inst. Canada, Toronto, Ontario, 6-8 May 1976, 1976.

331. Schoental, R. The Role of Nicotinamide and of Certain Other Modifying Factors in Diethylnitrosamine Carcinogenesis: Fusaria Mycotoxins and "Spontaneous" Tumors in Animals and Man. Cancer (Suppl.), 40(4):1835-1840, 1977.

332. Wattenberg, L. W., et al. Dietary Constituents Altering the Response to Chemical Carcinogens. Fed. Proc., 35:1327-1331, 1976.

333. Wattenberg, L. W. Inhibition of Chemical Carcinogenesis by Antioxidants and Some Additional Compounds. In: Fundamentals in Cancer Prevention, Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund (Tokyo, 1975), The Princess Takamatsu Cancer Research Fund, Tokyo, Japan, 1976. pp. 153-166.

334. Chowaniec, J., et al. Histology of Tumour Formation in the Bladder of Rats Receiving Dietary Saccharin and a Single Dose of n-Methyl n-Nitrosourea (Meeting Abstract). B. J. Cancer, 29(1):93, 1974.

335. Hicks, R. M., and J. Chowaniec. The Importance of Synergy Between Weak Carcinogens in the Induction of Bladder Cancer in Experimental Animals and Humans. Cancer Res., 37(8, Part 2):2943-2949, 1977.

336. Roe, F. J., et al. Feeding Studies on Sodium Cyclamate, Saccharin and Sucrose for Carcinogenic and Tumour-Promoting Activity. Food Cosmet. Toxicol., 8(2):135-145, 1970.

337. Nomura, T. Inhibitory Effect of Caffeine on Chemical Carcinogenesis in Mice (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:244, 1977.

338. Challis, B. C., and C. D. Bartlett. Possible Cocarcinogenic Effects of Coffee Constitutents. Nature (Lond.), 254(5500): 532-533, 1975.

339. Watanabe, K., et al. Effect of Bile Acids and Neutral Sterols on Benzo(a)pyrene-Induced Tumorigenesis in Skin of Mice: Brief Communication. J. Natl. Cancer Inst., 60(6): 1501-1503, 1978.

340. Altman, R. F., et al. Phospholipids Retard and Cholesterol Promotes the Formation of Tumours Induced by Carcinogenic Hydrocarbons. Z. Naturforsch. (B), 23(9):1277-1279, 1968.

341. Bingham, E., et al. Multiple Factors in Carcinogenesis. Ann. N.Y. Acad. Sci., 271:14-21, 1976.

342. Blunck, J. M., and C. E. Crowther. Enhancement of Azo Dye Carcinogenesis by Dietary Sodium Sulphate. Eur. J. Cancer, 11(1):23-31, 1975.

343. Homburger, F., and E. Boger. The Carcinogenicity of Essential Oils, Flavors, and Spices: A Review. Cancer Res., 28(11):2372-2374, 1968).

344. Salaman, M. H., and F. J. Roe. Cocarcinogenesis. Br. Med. Bull., 20(2):139-144, 1964.

345. Schramm, R., and W. Gibel. Carcinogenic and Cocarcinogenic Plant Products, II. Carcinogenic Substances Synthesized by Pteridophyta (Filicinae) and Spermatophyta (Cyadineae, Dicotyledoneae, Monocotyledoneae). Arch. Geschwulstforsch., 33(2):169-188, 1969.

346. Zschiesche, W., and G. Bruns. Carcinogenesis of 7-Ketocholesterol. Oncology, 18(4):289-299, 1964.

347. Bryson, G., and F. Bischoff. Triolein as a Cocarcinogen. Fed. Proc., 23(2, Pt. 1):106, 1964.

348. Dzagnidze, L. I., and P. N. Krasniyanskaya. A Study of Possible Carcinogenic and Cocarcinogenic Properties of Overheated Oils. Soobshch. Akad. Nauk. Gruz. SSR, 67(1): 229-231, 1972.

349. Dayton, S., et al. Effect of High-Oleic and High-Linoleic Safflower Oils on Mammary Tumors Induced in Rats by 7,12-Dimethylbenz(alpha)anthracene. J. Nutr., 107(8):1353-1360, August 1977.

350. Sinnhuber, R. O., et al. Metabolism and Cocarcinogenicity of Cyclopropenes. Oregon State Higher Educ. Sys., School of Agriculture, Food Science and Technology, Corvallis, Oregon.

351. Lee, D. J., et al. Synergism Between Cyclopropenoid Fatty Acids and Chemical Carcinogens in Rainbow Trout (Salmo Gairdneri). Cancer Res., 28(11):2312-2318, 1968.

352. Petering H. G. Diet, Nutrition, and Cancer. Adv. Exp. Med. Biol., 91:207-228, 1977.

353. Raikow, R. B. Effects of Carcinogens or Suspected Carcinogens on Viral Luekemogenesis in C57BL/10, SJL/J Mice and Their F1 Hybrid (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 19:23, 1978.

354. Rice, E. W. Furfural: Exogenous Precursor of Certain Urinary Furans and Possible Toxicologic Agent in Humans. Clin. Chem., 18(12):1550-1551, 1972.

355. Ruchkovskii, B. S., et al. Carcinogenic and Cocarcinogenic Action of Dried Fruit Extract. Vopr. Onkol., 20(4):58-61, 1974.

356. Rothman, K. J. The Effect of Alcohol Consumption on Risk of Cancer of the Head and Neck. (Head and Neck Cancer, State-of-the-Art Conference, St. Louis, Mo., February 16-18, 1976.) Laryngoscope, 88(1, Part 2, Suppl. 8):51-55, 1978.

357. Bross, I. D., and J. Coombs. Early Onset of Oral Cancer Among Women Who Smoke and Drink. Proc. Am. Assoc. Cancer Res., 17:1, 1976.

358. Gibel, W., and G. Wittig. On the Experimental Induction of Carcinoma of the Esophagus. Dtsch. Gesundheitsw., 19(14): 635-637, 1964.

359. Radike, M. J., et al. Effect of Ethanol and Vinyl Chloride on the Induction of Liver Tumors: Preliminary Report. Environ. Health Perspect., 21:153-155, 1977.

360. Jayant, K. Statistical Appraisal of the Association of Smoking and Chewing Habits to Oral and Pharyngeal Cancers. Indian J. Cancer, 14(4):293-299, 1977.

361. Ranadive, K. J., et al. Experimental Studies on Betel Nut and Tobacco Carcinogenicity. Int. J. Cancer, 17(4):469-476, 15 April 1976.

362. Hecht, S. S., et al. Chemical Studies on Tobacco Smoking Determination of Hydroxybenzyl Alcohols and Hydroxyphenyl Ethanols in Tobacco and Tobacco Smoke. J. Anal. Toxicol., 2(2):56-59, 1978.

363. DiPaolo, J. A., and P. J. Donovan. *In Vitro* Morphologic Transformation of Syrian Hamster Cells by U.V.-Irradiation is Enhanced by X-Irradiation and Unaffected by Chemical Carcinogens. Int. J. Radiat. Biol., 30(1):41-53, July 1976.

364. Palotay, J. L., et al. Carcinogen-Induced Cutaneous Neoplasms in Nonhuman Primates. J. Natl. Cancer Inst., 57(6):1269-1274, 1976.

365. Lohsoonthorn, P. The Epidemiologic Study of Subsite Large Bowel Cancer. Diss. Abstr. Int. (B), 36(9):4399-B, 1976.

366. Werner, B., et al. Cholecystectomy and Carcinoma of the Colon, An Experimental Study. Z. Krebsforsch., 88(3):223-230, 1977.

367. Williamson, R. C., et al. The Effect of Pancreatobiliary Diversion on Testical Carcinogenesis (Meeting Abstract). Br. J. Surg., 64(11):837, 1977.

368. Reddy, B. S. Role of Bile Metabolites in Colon Carcinogenesis. Cancer (Suppl.), 36:2401-2406, 1975.

369. Reddy, B. S., et al. Promoting Effect of Bile Acids on Colon Carcinogenesis in Germfree and Conventional Rats (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:119, 1977.

370. Wynder, E. L. Metabolic Epidemiology of Colon Cancer. Amer. Health Foundation, Inc., New York, New York.

371. Curtis, G. L., et al. Enhancement of 7,12-Dimethylbenzanthracene Skin Carcinogenesis by Adenosine, 3',5'-Cyclic Monophosphate. Cancer Res., 34(9):2192-2195, 1974.

372. Freund, H., et al. Breast Cancer Arising in Thoracotomy Scars (Letter to Editor). Lancet, 1(7950):97, 1976.

373. Glaser, A. Pathologic and Clinical Aspects of Bone Tumors. Zentralbl. Chir., 101(6):321-329, 1976.

374. Lung Cancer and Chronic Bronchitis. Med. M. Aust., 51(24): 926-927, 1964.

375. Stenback, F., and G. Curtis. Mechanism of Action of Polycyclic Hydrocarbon Carcinogens: Immunological Aspects (Meeting Abstract). Scand. J. Immunol., 6(11):1196, 1977.

376. Fukushima, S., et al. Effects of Foreign Bodies on Gastric Carcinogenesis in Rats Treated with n-Methyl-n'-nitro-n-nitrosoguanidine (MNNG). (Proc. Jpn. Cancer Assoc., 33rd Annual Meeting, October 1974.) Gann, 67, 1975.

377. Kogan, A. K. H., and V. I. Kulitskaia. The Effect of a Stationary Magnetic Field on Induced Carcinogenesis. Patol. Fiziol. Eksp. Ter., (2):63-68, 1977.

378. Suzuki, S. Effect of Rotary Motion on Carcinogenesis. J. Nagoya City Univ. Med. Assoc., 19(4):1517-1558, 1969.

379. Harris, C. C. The Carcinogenicity of Anticancer Drugs: A Hazard in Man. Cancer, 37(2):1014-1023, 1976.

380. Arseneau, J. C., et al. Synergistic Carcinogenic Effect of Procarbazine and Ionizing Radiation in CDF Mice. Proc. Am. Assoc. Cancer Res., 16:120, 1975.

381. Kosir, A. Contribution of Carcinogenesis. Acta Med. Iugosl., 16(2):172-180, 1962.

382. Medina, D. Enhancement of Mammary Tumor Formation in Mice by a Cytostatic Drug, Melphalan. Cancer Res., 37(1):317-319, 1977.

383. Wang, C. Y., and S. Hayashide. Enhancement of N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) Carcinogenicity for Rat Urinary Bladder by Allopurinol. Proc. Am. Assoc. Cancer Res., 17:149, 1976.

384. Maize, J. C. Skin Cancer in Immunosuppressed Patients. JAMA, 237(17):1857-1858, 1977.

385. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 10, 1976. pp. 153-161.

386. Vesselinovitch, S. D., and N. Mihailovich. The Inhibitory Effect of Griseofulvin on the "Promotion" of Skin Carcinogenesis. Cancer Res., 28(12):2463-2465, 1968.

387. Langbein, W. Contribution to the Cocancerogenic Effect of Cignolin in Animals. Radiobiol. Radiother. (Berl.), 13(2):233-240, 1972.

388. Weisburger, J. H., et al. Modification of Diethylnitrosamine Liver Carcinogenesis with Phenobarbital but Not with Immunosuppression. J. Natl. Cancer inst., 54(5):1185-1188, 1975.

389. Kitagawa, T., and H. Sugano. Enhancement of Azo-Dye Hepatocarcinogenesis with Dietary Phenobarbital in Rats. Gann, 68(2):255-256, 1977.

390. Van Duuren, B. L. Tumor-Promoting and Cocarcinogenic Agents in Chemical Carcinogenesis. In: Chemical Carcinogens, Searle, C. E., ed., American Chemical Society Monograph 1973, American Chemical Society, Washington, D.C., 1976. pp. 24-51.

391. Slaga, T. J., et al. Mechanism of Action of Steroidal Anti-Inflammatory Agents that Inhibit Skin Carcinogenesis. Proc. Am. Assoc. Cancer Res., 16:37, 1975.

392. Kawaguchi, K. Studies on Experimental Induction of Endometrial Carcinoma in Rabbits, Especially Related to Their Carcinogenesis (Meeting Abstract). Acta Obstet. Gynaecol. Jpn., 21(1):68, 1976.

393. Muhlbock, O., and L. M. Boot. The Mode of Action of Ovarian Hormones in the Induction of Mammary Cancer in Mice. Biochem. Pharmacol., 16(4):627-630, 1967.

394. Warren, S., and O. Gates. Radiation Carcinogenesis, Progress Report IV, 15 March 1976 - 15 May 1977. Available through National Technical Information Service, Springfield, VA, as C00-3017-31, EY-76-S-02-3017, 1977. 15 pp.

395. Lee, C., et al. *In Vitro* Interaction of Estrogen and Prolactin on Hormone-Dependent Rat Mammary Tumors (38511). Proc. Soc. Exp. Biol. Med., 148(1):224-226, 1975.

396. Forsberg, J. G., and L. S. Breistein. A Synergistic Effect of Oestradiol and Prolactin Influencing the Incidence of 3-Methylcholanthrene Induced Cervical Carcinomas in Mice. Acta Pathol. Microbiol. Scand (A), 84(5):384-390, 1976.

397. Vorherr, H. Contraception Postabortion and Postpartum, Advantages and Disadvantages of Hormonal Contraceptive with Particular Reference to the Relationship Between Female Sex Hormones and Thromboembolism and Carcinoma of the Breast and Genitals. Gynaekol. Rundsch., 15(1):48-73, 1975.

398. Lemon, H. M. Estriol and Prevention of Mammary Carcinoma. Cancer Detec. Prevent., 1(2):263-281, 1976.

399. Welsch. C. W. Effects of a Norethynodrel-Mestranol Combination (ENOVID) on Development and Growth of Carcinogen-Induced Mammary Tumors in Female Rats. Cancer, 23(3):601-607, 1969.

400. Chevrel, B. Role of Steroid Hormones in the Development of Malignant Tumors (Letter to Editor). Nouv. Presse. Med., 5(17):1145, 1976.

401. Gurkalo, B. K., and M. A. Zabezhinsky. Modification of Chemical Carcinogenesis with Adrenergic Compounds. Vestn. Akad. Med. Nauk SSSR, (2):38-42, 1978.

402. Schmeltz, I., et al. Formation and Determination of Naphthalenes in Cigarette Smoke. Anal. Chem., 48(4):645-650, 1976.

403. Argus, M. F., and J. C. Arcos. Hydrocarbon-Nitrosamine Synergism as a Possible Amplying Factor in Lung Tumorigenesis by Tobacco Smoke. J. Theor. Biol., 56(2):491-498, 1976.

404. Bock, F. G. Cocarcinogenic Activity of Nicotine. Proc. Am. Assoc. Cancer Res., 17:2, 1976.

405. Etiology of Nasopharyngeal Carcinoma. Lancet, 2(8000):1393, 1976.

406. DeMicco-Pagis, C., et al. Pathologic and Ultrastructural Investigation of a DMBA-Induced Transplantable Melanoma in the Golden Hamster. Bull Cancer (Paris), 63(1):73-86, 1976.

407. Stepanova, L. G., et al. DNA Reparation and Chromosome Aberrations in Human Cells Infected with LPV Oncornavirus. Vopr. Virusol., (6):712-716, 1977.

408. Bryan, W. R. Current Concepts of Viral Neoplasia. South. Med. J., 57(11):1263-1267, 1964.

409. Mazzucco, K. The Effect of Various Solvents (Benzene, Toluene, Acetone) Used with Carcinogens on the Collagen Content of the Mouse Dorsal Skin. Osterr. Z. Onkol., 2(2-3):49-51, 1975.

410. Bingham, E., and H. L. Falk. Environmental Carcinogens, The Modifying Effect of Cocarcinogens on the Threshold Response. Arch. Environ. Health, 19(6):779-783, 1969.

411. Bingham, E., and P. J. Nord. Cocarcinogenic Effects of n-Alkanes and Ultraviolet Light on Mice. J. Natl. Cancer Inst., 58(4):1099-1101, 1977.

412. Tanaka, T. Influence of n-Dodecane on Rats Exposed Transplacentially to Benzo(a)pyrene and Nitrosomethylurethan During Pregnancy (Meeting Abstract). Third International Symposium on Detection and Prevention of Cancer, 1976. pp. 286-287.

413. Horton, A. W. Cellular Mechanisms of Chemical Carcinogenesis. National Technical Information Service No. PB 225 631, 1973. 91 pp.

414. Mori, H., et al. Effect of Carbon Tetrachloride on Carcinogenicity of Petasites Japonicus, and Transplantability of Induced Tumors. Gann, 68(6):841-845, 1977.

415. Mirme, H. Modifying Effect of Water-Soluble Shale Phenols on Carcinogenesis. Vopr. Profil. Zagryaz. Okruzhayushchei. Chel. Sredy Kantserogennymi Veshchestvami; 16-18, 1972.

416. Hecker, E. Aspects of Cocarcinogenesis. In: Scientific Foundations of Oncology, T. Symington and R. L. Carter, eds., William Heinemann Medical Books, Ltd., Chicago, 1976. pp. 310-318.

417. Falk, H. L. Possible Mechanisms of Combination Effects in Chemical Carcinogenesis. Oncology, 33(2):77-85, 1976.

418. Pershagen, G., et al. Mortality in a Region Surrounding an Arsenic Emitting Plant. Environ. Health Perspect., 19:133-137, 1977.

419. Gargus, J. L., et al. Utilization of Newborn Mice in the Bioassay of Chemical Carcinogens. Toxicol. Appl. Pharmacol., 15(3):552-559, 1969.

420. Sakharov, I. I., et al. The Cocarcinogenic Activity of Sulfonol NP-1. Gig. Tr. Prof. Zabol., (9):56-58, 1973.

421. Pyleva, Z. A., et al. Data on the Biological Properties of Olefin Sulfate. Vopr. Onkol., 24(1):55-60, 1978.

422. Loewengart, G., and B. L. Van Duuren. Evaluation of Chemical Flame Retardants for Carcinogenic Potential. J. Toxicol. Environ. Health, 2(3):539-546, 1977.

423. Arrhenius, E., et al. Disturbance of Microsomal Detoxication Mechanisms in Liver by Chlorophenol Pesticides. Chem. Biol. Interact., 18(1):35-46, 1977.

424. Arkhipov, G. N., and I. N. Kozlova. Study of the Carcinogenic Properties of the Herbicide, Amine Salt of 2,4-Dicholorphenoxyacetic Acid. Vopr. Pitan., (5):83-84, 1974.

425. Uchiyama, M., et al. Cocarcinogenic Effect of DDT and PCB Feeding on Methylcholanthrene-Induced Chemical Carcinogenesis. Bull. Environ. Contam. Toxicol., 12(6):687-693, 1974.

426. Nagasaki, H., et al. Analysis of Various Factors on Liver Carcinogenesis in Mice Induced by Benzene Hexachloride (BHC) and Technical Polychlorinated Biphenyls (PCBs). J. Nara. Med. Assoc., 25(6):635-648, 1974 (Recd. 1975).

427. Capuco, A. V. Ammonia: A Modulator of 3T3 Cell Growth. Diss. Abstr. Inst. (B), 38(9):4085, 1978.

428. Rubin, D., and I. S. Levij. Chemical Carcinogenesis in the Hamster Cheek Pouch: Influence of Inhibitors and Inducers of Alkaline Phosphatase. Pathol. Microbiol. (Basel), 43(1):26-30, 1975.

429. Lane, B. P., and M. J. Mass. Carcinogenicity and Cocarcinogenicity of Chromium Carbonyl in Heterotopic Tracheal Grafts. Cancer Res., 37(5):1476-1479, 1977.

430. Hayatsu, H., et al. Potential Cocarcinogenicity of Sodium Hypochlorite. Nature (Lond.), 233(5320):495, 1971.

431. Nagata, C., et al. Effect of Hydrogen Peroxide, Fenton's Reagent, and Iron Ions on the Carcinogenicity of 3,4-Benzopyrene. Gann, 64(3):277-285, 1973.

432. Deichmann, W. B., and J. L. Radomski. Synergism Among Oral Carcinogens and Tumorigens, Report of Preliminary Experiments. Toxicol. Appl. Pharmacol., 6(3):343-344, 1964.

433. Breedin, P. H., and D. H. Buss. Ferruginous (Asbestos) Bodies in the Lungs of Rural Dwellers, Urban Dwellers, and Patients with Pulmonary Neoplasms. South. Med. J., 69(4):401-404, 1976.

434. Einbrodt, H. J. Combined Effort of Fine Dust on the Lung. Staub Reinhaltung Luft, 36(3):122-126, 1976.

435. Rom, W. N., and A. M. Langer. Carcinogenicity of Fibrous Glass (Letter to Editor). West. J. Med., 126(5):413, 1977.

436. Nordenson, I., et al. Occupational and Environmental Risks in and Around a Smelter in Norther Sweden, II. Chromosomal Aberrations in Workers Exposed to Arsenic. Hereditas, 88(1):47-50, 1978.

437. Ishinishi, N., et al. Preliminary Experimental Study on Carcinogenicity of Arsenic Trioxide in Rat Lung. Environ. Health Perspect., 19:191-196, 1977.

438. Uzawa, T. Histopathological Studies on Pulmonary Reaction by Beryllium Oxide in Rat (Experimental Tumorous Action of BEO Combined with Carcinogenic Hydrocarbons). Bull. Tokyo Med. Dent. Univ., 9(3):440, 1963.

439. Nettesheim, P., et al. Carcinogenic and Cocarcinogenic Effects of Inhaled Synthetic Smog and Ferric Oxide Particles. J. Natl. Cancer Inst., 55(1):159-169, 1975.

440. Sellakumar, A., et al. Effects of Different Dusts on Respiratory Carcinogenesis in Hamsters Induced by Benzo(a)pyrene and Diethylnitrosamine. Eur. J. Cancer, 12(4): 313-319, 1976.

441. Bock, F. G., et al. Cocarcinogenic Activity of Peroxy Compounds. J. Natl. Cancer Inst., 55(6):1359-1361, 1975.

442. Kripke, M. L., and T. Borsos. Accelerated Development of Benzo(a)pyrene-Induced Skin Tumors in Mice Treated with Pyran Copolymer. J. Natl. Cancer. Inst., 53(5):1409-1410, 1974.

443. Shapiro, R. Genetic Effects of Bisulfite (Sulfur Dioxide). Mutat. Res., 39(2):149-176, 1977.

444. Calop, J., et al. A Study of the Influence of Trace Elements on the Hydroxylation of Benzo(a)pyrene. Eur. J. Toxicol. Environ. Hyg., 9(5):271-286, 1976.

445. Shimkin, M. B., et al. Lung Tumor Response in Mice to Metals and Metal Salts. Adv. Exp. Med. Biol., 91:85-91, 1977.

446. Kobayashi, N., and T. Okamoto. Effects of Lead Oxide on the Induction of Lung Tumors in Syrian Hamsters. J. Natl. Cancer Inst., 52(5):1605-1610, 1974.

447. Cardesa, A., et al. The Syncarcinogenic Effect of Methylcholanthrene and Dimethylnitrosamine in Swiss Mice Z. Krebsforsch., 79(2):98-107, 1973.

448. Danz, M., et al. Prevention of 2-Acetylaminofluorene-Induced Extrahepatic Short-Term Effects by 3-Methylcholanthrene. Exp. Pathol. (Jena), 13(4-5):262-267, 1977.

449. Cardesa, A., et al. Effects of Intraperitoneal Injections of Dimethyl- and Diethylnitrosamine, Alone or Simultaneously on Swiss Mice. Z. Krebsforsch., 82(3):233-238, 1974.

450. Topping, D. C., et al. The Interaction of Benzo(a)pyrene and Benzo(e)pyrene in Respiratory Tract Carcinogenesis (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 19:43, 1978.

451. Mondal, S., et al. Syncarcinogensis in Cultured C3H/10T1/2 Cells (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:8, 1977.

452. Palmer, M. S., et al. Effect of Ozone on Benzpyrene Hydroxylase Activity in the Syrian Golden Hamster. Cancer Res., 31(6):730-733, 1971.

453. Sellakumar, A. R., et al. Influence of Croton Oil in Hamster Lung Carcinogenesis. Proc. Am. Assoc. Cancer Res., 16:57, 1975.

454. Hecker, E. Cocarcinogenic Agents Derived from Euphorbiaceae. Planta. Med., 1968:24-25, 1968.

455. Hecker, E. New Toxic, Irritant, and Cocarcinogenic Diterpene Esters from Euphorbiaceae and from Thymelaeaceae. Pure Appl. Chem., 59(9):1423-1431, 1977.

456. zor Hausen, H. Z., et al. Persisting Oncogenic Herpesvirus Induced by the Tumour Promoter TPA. Nature (Lond.), 272(5651):373-375, 1978.

457. Komitowski, D., et al. Epidermal Intercellular Relationships During Carcinogenesis and Cocarcinogenesis as Revealed by Scanning Electron Microscopy. Virchows Arch. (Cell Pathol.), 24(4):317-333, 1977.

458. Janoff, A., et al. Local Vascular Changes Induced by the Cocarcinogen, Phorbol Myristate Acetate. Cancer Res., 30(10):2567-2571, 1970.

459. Soper, C. J., and F. J. Evans. Investigations into the Mode of Action of the Cocarcinogen 12-O-Tetradecanoylphorbol-13-acetate Using Auxotrophic Bacteria. Cancer Res., 37(8, Part 1):2487-2491, 1977.

460. Tsuda, H., et al. Synergistic Effect of Urinary Bladder Carcinogenesis in Rats Treated With n-Butyl-N-(4-hydroxybutyl)nitrosamine, n-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide, n-2-Fluorenylacetamide, and 3,3'-Dichlorobenzidine. Gann, 68(2):183-192, 1977.

461. Kallistratos, G. Prevention of 3,4-Benzpyrene Carcinogenesis by Naturally Occurring and Synthetic Compounds. Muench. Med. Wochenschr., 117(10):391-394, 1975.

462. Truhaut, R., et al. Inhibitor Effect of Ellipticine [Dimethyl-5, II-(6H) Pyrido (4,3-B Carbazole) on Rat Liver Carcinogenesis Induced by BT6 (n,n-Dimethyl-*p*-benzothiazolylazo) Aniline]: Incidences on Cytochrome P450 and Arginase Activity (Meeting Abstract). Fourth Meeting of the European Association for Cancer Research (held at Universite de Lyon, September 13-15, 1977), European Association for Cancer Research, Lyon, France, 1977. p. 86.

APPENDIX A

A REVIEW OF THE CARCINOGEN LITERATURE OF 125 CHEMICALS

INTRODUCTION

The first task of EPA Contract 68-02-2773 is to identify 20 significant atmospheric carcinogens. Sampling and analytical methodology based on porous polymer sorbents and gas chromatography/mass spectrometry will then be developed for 15 of these chemicals.

In order to identify significant carcinogens, the literature has been reviewed for about 125 chemicals to determine whether they should be considered carcinogens for this project. The results for each chemical are given in this appendix. An index to the chemicals precedes the results.

Different criteria must be used to define what test results indicate carcinogenicity depending on the use for which the resulting list is intended. For this program, some chemicals have been included on the possible carcinogen list based on a limited amount of short-term mutagenicity data. If these lists should be used for other purposes, it would be expedient to review the literature cited and draw the appropriate conclusions based on other guidelines.

For this project, a probable carcinogen generally has at least some positive animal data coupled with positive mutagenicity data from at least one well-established mutagenicity test or several mutagenicity tests which have not been as extensively validated. The mutagenicity tests which were considered fairly well established include the Ames *Salmonella typhimurium* test and the enhancement of viral transformation tests (e.g., B. C. Casto), with the *E. coli* (pol A) differential toxicity and the *Drosophila* tests also considered important.

Animal carcinogenicity tests were considered less significant if they were conducted more than 5 to 10 years ago, tested by the subcutaneous route of administration demonstrating only local tumors, utilized only a few animals, or reported no concurrent control animals.

Dr. B. C. Casto, BioLabs, Inc., Northbrook, Illinois, has been a consultant for Monsanto Research Corporation on this EPA contract.

INDEX

Chemical	Page
Acetaldehyde	86
Acetone	87
Acetonitrile	88
Acrolein	89
Acrylonitrile	90
Aldrin	91
Allyl Chloride	92
Aniline	93
Anthracene	94
Benz(a)anthracene	95
Benzene	96
Benzidine	97
Benzo(a)pyrene	98
Benzoquinone (Quinone)	99
Benzoyl Peroxide	100
Benzyl Chloride	101
Biphenyl	102
Bis(chloromethyl) Ether	103
Butadiene	104
Captan	105
Carbon Disulfide	106
Carbon Tetrachloride	107
Chloracetic Acid	108
Chlordane	109
Cresols	110
Chlorobenzilate	111
Chloroform	112
Chloroprene	113
Chloropropane	115
Chrysene	116
Cumene Hydroperoxide	117
DDT	118
Di-tert-butyl Peroxide	119
Di(2-ethylhexyl) Phthalate	120
2,4-Diaminoanisole	122
Diazinon	124
o-Dichlorobenzene	125
p-Dichlorobenzene	126
Dichlorobenzidine	127
Dichlorobutene	128
Dichlorodifluoromethane	129
1,1-Dichloroethane	130
Dichloronaphthoquinone	131
Dichlorophenol	132
Dichloropropene	133
Dichloropropionic Acid	134
Dichlorovinyl Dimethyl Phosphate (Dichlorvos)	135
Dimethylacetamide	136

Index - Continued

Chemical	Page
Dimethylamine	137
Dimethylhydrazine	138
Dinitrotoluene	139
Dioxane	140
Diphenyl Oxide	141
Disodium Methanearsonate	142
Dursban	143
Endosulfan	144
Endrin	145
Epichlorohydrin	146
Eptam	147
Ethanol	148
Ethylbenzene	149
Ethylene	150
Ethylene Dibromide	151
Ethylene Dichloride	152
Ethylene Glycol	153
Ethylene Oxide	154
Ethylenimine	155
Fluoranthene	156
Formaldehyde	157
Guthion	158
Heptachlor	159
Hexachlorobenzene	160
Hexachlorobutadiene	161
Hexamethylenetetramine	162
Hydrazine	163
Hydroquinone	164
Kelthane	165
Malathion	166
Maleic Anhydride	167
Mercaptobenzothiazole	168
Methyl Bromide	169
Methyl Chloride	170
Methyl Ethyl Ketone	171
Methyl Methacrylate	172
4,4'-Methylene Bis(2-chloroaniline)	173
Methylene Chloride	174
Methylenedianiline	175
Methylstyrene	176
Morpholine	177
Naphtha	178
1-Naphthylamine	179
Naphthalene	180
Naphthoquinone	181
1-Naphthyl Methylcarbamate	182
Nitrobenzene	183
Nitrophenol	184

Index - Continued

Chemical	Page
Nitrosodimethylamine	185
Nitrochlorobenzene	186
Parathion	187
Pentane	188
Pentachlorophenol	189
Phenol	190
Polychlorinated Biphenyls	191
Propanol	192
Propylene Oxide	193
Pyrene	194
Sorbic Acid	195
Styrene	196
Sulfolane	197
Tetrabromoethane	198
Tetrachloroethane	199
Tetrachloroethylene	200
Tetraethyl Lead	201
Toluene	202
Toluene Diisocyanate	203
Toluenediamine	204
Toxaphene	205
Trichlorfon	206
Trichloroethane	207
Trichloroethylene	208
Trichlorofluoromethane	209
Trichlorophenol	210
Urethane	211
Vinyl Acetate	212
Vinyl Bromide	213
Vinyl Chloride	214
Vinylidene Chloride	215
Xylene	216

Acetaldehyde

Acetaldehyde is possibly a carcinogen promoter [25], but no references to it as a carcinogen or mutagen were found in TOXLINE or CANCERLINE. Two references by Nakahara and Mori in 1939 and 1940, as reported by Hartwell [26], demonstrated no tumors in rats fed acetaldehyde in their food for more than 300 days. It is probably not a carcinogen.

---

[25] Davies, J. C. Co-Carcinogenesis with respect to the Contents of Cigarette Tobacco. R. Soc. Health J., 93(6):296-301, 1973.

[26] Hartwell, J. L. Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Second Edition. National Technical Information Service No. PB 216 478, 1951.

Acetone

Acetone [2-propanone, dimethyl ketone, Chemical Abstract Service (CAS) No. 67-64-1] has been extensively tested for carcinogenic activity both by itself and as a negative solvent control for other chemicals [5]. No significant positive results could be found on CANCERLINE or TOXLINE for acetone. It is also negative on most *in vitro* tests and is used as a negative solvent control for many chemicals in these tests.

Acetonitrile

The only data suggesting that acetonitrile is a carcinogen are equivocal results from a 2-year rat study [6]. It is considered a noncarcinogen for this project.

Acrolein

Acrolein appears to be toxic and reduces ciliary action of the bronchial epithelium [27, 28], but it is not mutagenic in *S. cerevisiae* [29] or dominant lethal mice tests [30]. Acrolein has been found to be a mutagen to the TA1538 and TA98 strains of *S. typhimurium* [31]. It will be considered to be a possible carcinogen for this project.

Production and Persistence

It is estimated that 6.5×10^7 kg is emitted per year, primarily associated with acrylic acid manufacture [1]. Other estimates are 4.2×10^5 kg/yr released from 2.8×10^7 kg produced [6] and a production of 2.8×10^7 kg produced in 1974 with a 6.7% growth forecast through 1979 [32]. It has an atmospheric half-life estimated at 2.6 hours [8]. Its boiling point is -88°C and it has a vapor pressure of 220 mm at 20°C [33].

---

[27] Shabad, L. M., et al. The Feasibility of Preventing the Effects of Carcinogens on Man. Kazan Med. Zh, (5):92-93, 1973.

[28] Terrell, J. H., and I. Schmeltz. Cigarettes: Chemical Effect of Sodium Nitrate Content. Science, 160:1456, 1968.

[29] Izard, C. Mutagenic Effects of Acrolein and its Two Epoxides, Glycidol, and Glycidal, in *Saccharomyces Cerevisiae*. C. R. Acad. Sci., Ser. D., 276(23):3037-3040, 1973.

[30] Epstein, S. S., et al. Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse. Toxicol. Appl. Pharmacol., 23:288-325, 1972.

[31] Bignami, M., et al. Relationship Between Chemical Structure and Mutagenic Activity in Some Pesticides: The Use of *Salmonella Typhimurium* and *Aspergillus Nidulans*. Mutat. Res., 46(3):243-244, 1977.

[32] Allport, J., et al. A Study of Industrial Data on Candidate Chemicals for Testing. National Technical Information Service No. PB 274 264, 1977.

[33] Verschueren, K. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Co., New York, 1977.

Acrylonitrile

Positive Ames tests [34], *E. coli* mutation tests [35], and viral transformation enhancement tests (personal communication with B. C. Casto on 9 February 1978) have been reported along with negative recessive lethal *Drosphila melanogaster* and negative *Vicia faba* chromosome aberration tests [32]. Human epidemiological evidence points toward acrylonitrile being a carcinogen [36]. Additionally, a 1-year interim report from the Manufacturing Chemists Association of ongoing ingestion and inhalation studies of acrylonitrile in laboratory rats reports the rats developing a variety of tumors including carcinomas [37]. Based on these findings, acrylonitrile is being placed on the probable carcinogen list for this project.

Production and Persistence

It is estimated that 3.7×10^5 kg is emitted per year [1]. (Another estimate is 9.6×10^6 kg per year [6].) Acrylonitrile has a boiling point of 77°C and a vapor pressure of 100 mm at 23°C [33].

---

[34] Milvey, P., and M. Wolff. Mutagenic Studies with Acrylonitrile. Mutat. Res., 48(3-4):271-278, 1977.

[35] Venitt, S., et al. Mutagenicity of Acrylonitrile (Cyanoethylene) in *Escherichia Coli*. Mutat. Res., 45:283-288, 1977.

[36] Acrylonitrile Linked to Cancer in Workers. Chem. Eng. News, 55:6, 1977.

[37] Finklea, J. F. Acrylonitrile. Am. Ind. Hyg. Assoc. J., 38:417-422, 1977.

Aldrin

Aldrin has been found to cause neoplasia in two strains of mice [38] and tumors in weanling rats [39]. Aldrin is converted into dieldrin in the environment [40], and dieldrin is a carcinogen at 0.1 ppm in dietary exposure to mice [41]. Thus the sale and production of aldrin was suspended [42]. Many other animal studies have been conducted with questionable results [43], and some *in vitro* tests have been negative [18]. Since there are enough data to suspend production of aldrin, it will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 4.5 x 10^6 kg aldrin were produced in 1971 [43]. Another production estimate is 1.1 x 10^7 kg/year (1976) [6].

---

[38] Song, J., and W. E. Harville. Carcinogenicity of Aldrin and Dieldrin on Mouse and Rat Liver. Fed. Proc., 23:336, 1964.

[39] Diechmann, W. B., et al. Tumorigenicity of Aldrin, Dieldrin, and Endrin in the Albino Rat. Ind. Med Surg., 39(10): 426-434, 1950.

[40] Wurster, C. F. Aldrin and Dieldrin. Environment, 13(8): 33-45, 1971.

[41] Epstein, S. S. Prevention - Environmental Exposure: An Overview, Including the Role of Pesticides. Third International Symposium on Detection and Prevention of Cancer, 1976. p. 5.

[42] Epstein, S. S. Case Study 5: Aldrin and Dieldrin Suspension Based on Experimental Evidence and Evaluation and Societal Needs. Ann. N.Y. Acad. Sci., 271:187-195, 1976.

[43] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 25-38.

Allyl Chloride

Allyl chloride (3-chloropropene, CAS No. 107-05-1) is on the NIOSH Safety Alert List. No references have been found on TOXLINE, CANCERLINE, or in the Stanford Research Institute study on hazard priority ranking [7], to indicate that allyl chloride is a carcinogen or mutagen. A recent reference, however, reports that allyl chloride is a mutagen in *S. typhimurium*, *S. cerevisiae*, and *E. coli* test systems [9]. It is therefore classified as a possible carcinogen for this project.

Production and Persistence

It is estimated that 4.2×10^5 kg is emitted per year from stationary sources [1]. Another estimate is 2×10^6 kg released from a production of 1.3×10^8 kg per year [44], and a production estimate of 1.3×10^8 kg in 1972 [6]. It is reported to take 27 minutes for 50% of the allyl chloride in a 1-ppm solution to evaporate at 25°C [33]. It has a half-life with HO radical of 21 hours and with O_3 radicals of 9 hours, and it hydrolyzes with a half-life of 7 days [44]. It has a boiling point of 45°C, a vapor pressure of 340 mm at 20°C, and a solubility of 3.3 g/l [33].

---

[44] Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 164, 1975.

Aniline

The IARC monograph on aniline [45] reports that aniline is probably not a carcinogen and that what early researches believed was cancer from aniline was most likely due to impurities such as benzidine. It has tested negative on a differential growth *E. coli* test (pol A) [46] and on *S. typhimurium* strains TA1535, 1537, 100, and 98 with and without microsomes [32]. It has also been reported negative in reversion to prototrophy in *Aspergillus nidulans* ($meth_3^-$) and several other tests [32]. It was classified negative/inadequate in one of the latest reviews [32] and will be considered a probable noncarcinogen for this project.

---

[45] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 27-36.

[46] Fluck, E. R., et al. Evaluation of a DNA Polymerase-Deficient Mutant of *E. Coli* for the Rapid Detection of Carcinogens. Chem. Biol. Interact., 15:219-231, 1976.

Anthracene

Anthracene is on the NIOSH Suspected Carcinogen List because of two 1955 references. In the first one [47], anthracene was found to be noncarcinogenic orally and interpertioneally. But when injected in 550 doses over a 2- to 3-year period (6 times/ week - total dose 4.5 g/rat), 5 out of 9 rats developed local fibrosarcomas. It is now known that multiple injections can sometimes cause fibrosarcomas. Recent studies [48] have shown anthracene to be a noncarcinogen and it is presently being used as a noncarcinogenic standard on studies to develop short-term assays for carcinogens [49-52].

---

[47] Schmall, D. Prufung von Naphthalin and Anthracen auf Carcerogene Wirking an Ratten. Zeitschrift fur Krebsforschung, 60:697-710, 1955.

[48] Stanton, M. F., et al. J. Natl. Cancer Institute, 49(3): 867-877, 1972.

[49] Pienta, R. J., et al. Morophological Transformation of Early Passage Golden Syrian Hamster Embryo Cells Derived from Cryopreserved Primary Cultures as a Reliable *in Vitro* Bioassay for Identifying Diverse Carcinogens. Int. J. Cancer, 19:642-655, 1977.

[50] DiPaolo, J. A., et al. Quantitation of Chemically Induced Neoplastic Transformation of BALB/3T3 Cloned Cell Lines. Cancer Research, 32:2686-2695, 1972.

[51] Purchase, I. F. H., et al. Evaluation of Six Short-Term Tests for Detecting Organic Chemical Carcinogens and Recommendations for Their Use. Nature, 264:624-627, 1976.

[52] McCann, J., et al. Detection of Carcinogens as Mutagens in the *Salmonella*/Microsome Test, Assay of 300 Chemicals. Proc. Natl. Acad. Sci. (USA), 72:5135-5139, 1975.

Benz(a)anthracene

Benz(a)anthracene (1,2-benzanthracene, CAS No. 56-55-3) is well known as a carcinogen. It is carcinogenic orally, subcutaneously and topically for mice [53]. It is one of the standard carcinogens used to evaluate the validity of short-term tests and will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that less than 100 kg/year is emitted from carbon black furnaces, the only stationary source cited for this chemical [1]. It is emitted in the exhaust from gasoline engines (61.7 mg/kg exhaust tar) and diesel engines (2.3-15 $\mu g/m^3$ exhaust) [53]. It has been detected in the air, soil, food, and cigarette smoke condensate [53]. It has a boiling point of 400°C [53].

---

[53] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3, 1973. pp. 45-68.

Benzene

Benzene (CAS No. 71-43-2) is one of the industrial substances suspected of carcinogenic potential to man as listed by the American Conference of Governmental Industrial Hygienists [54], and it will soon be controlled as a carcinogen. The International Agency for Research on Cancer [55] reports animal data which "do not permit the conclusion that carcinogenic activity has been demonstrated." In human data they support a relationship between exposure to benzene or benzene mixtures and the development of leukemia. Along with some positive studies [56], many references occur in the literatuare where benzene is a negative solvent control in animal studies [5]. In spite of these references, it is believed that benzene induces chromosomal damage in animals and man [32] and is a known carcinogen. An assessment of the air pollution aspects of benzene has been conducted [57]. Since benzene is being controlled as a carcinogen, it will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1 x 10^8 kg benzene is emitted per year, with solvent evaporation from degreasing operations contributing over 70% of the total [1]. Another estimate is 4 x 10^7 kg per year released from commercial uses of benzene [56]. It reacts rapidly with HO ($t_{1/2}$ = 3 days) but slowly with RO_2 and O_3 and has a 12.5 log partition coefficient [56]. Its boiling point is 80.1°C and it has a vapor pressure of 76 mm at 20°C [33].

---

[54] TLVs® Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1977. American Conference of Government Industrial Hygienists, 1977.

[55] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 203-222.

[56] Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 162, 1975.

[57] Walker, P. Air Pollution Assessment of Benzene. National Technical Information Service No. PB 256 734, 1976.

Benzidine

Benzidine is reported to be carcinogenic in the mouse, rat, hamster, and possibly in the dog [58]. Given orally, it has produced bladder carcinoma in the dog after a long latent period and liver tumors in the rat and hamster. Benzidine was a carcinogen to mice when given either by stomach intubation or in food [59]. These references, along with many others in TOXLINE and CANCERLINE show that benzidine should be considered a probable carcinogen.

Production and Persistence

It is estimated that 4.7×10^6 kg is produced per year [6]. A release factor of 0.015 is assumed which would give 7×10^4 kg released per year. This is probably too high since benzidine is well known as a carcinogen. Perhaps 7×10^3 kg would be closer to reality. It reacts with OH and O_3 with a $t_{1/2}$ of 1 day [60]. It has a boiling point of 402°C [33] and can be sublimed [58].

---

[58] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 80-86.

[59] Vesselinovitch, S. D., et al. Factors Modulating Benzidine Carcinogenicity Bioassay. Cancer Res., 35(10):2814-2819, 1975.

[60] Brown, S. L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals. National Technical Information Service No. PB 263 163, 1975.

Benzo(a)pyrene

Benzo(a)pyrene (3,4-benzpyrene, CAS No. 50-32-8) is well-established carcinogen following many different administrations including oral, skin, subcutaneous and intratracheal routes [61]. Positive results have been reported with mice, rats, guinea pigs, monkeys, newts, hamsters, and ducks [61]. It will be considered a probable carcinogen for this project.

Production and Persistence

Although not manufactured in quantity, it is a byproduct of combustion. It is estimated that 8.3 x 10^5 kg per year is released from stationary sources, with 96% of this coming from: (1) coal refuse piles, outcrops and abandoned mines, (2) residential external combustion of bituminous coal, (3) coke manufacture, and (4) residential external combustion of anthracite coal [1]. It has a boiling point of 311°C at 10 mm and 475°C at 760 mm [61].

---

[61] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3, 1973. pp. 91-136.

Benzoquinone (Quinone)

Japanese references from 1940 [62] and 1941 (as reported in Reference 5) state that 3/87 mice painted with benzoquinone (in benzene) developed skin cancer with 9/87 papillomas after 200 days compared to 0/46 skin cancers and 1/46 papillomas for the benzene control. Skin painting with a benzene solution in 1953 was said to cause 16/80 ear duct carcinomas [63]. In 1954 an 1956, inhalation experiments with a total of 50 treated mice were conducted with negative results [64]. By subcutaneous injection, 24 rats were tested with negative results in 1957 [64].

More recent references show that benzoquinone does not decrease hatchability of the *Drosophila melanogaster* [65], is not mutagenic toward *Drosophila* or cultured human leukocytes [65], produces no increase in recessive sex-lined lethan mutations in *Drosophila*, and did not significantly alter the rate of chromated translocations or breaks in leukocytes [66]. No other significant data were found in TOXLINE, CANCERLINE, or Reference 5. Benzoquinone is therefore to be considered a probable noncarcinogen for this project.

---

[62] Takizawa, N. On the Carcinogenic Action of Certain Quinones. Proc. Imperial Acad. (Tokyo), 16:309-312, 1940.

[63] Tiedmann, H. Ztschr. Naturforsch., 8b:49-50, 1953.

[64] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 1977. pp. 255-264.

[65] Vogel, E. Differential Sensitivity of Immature and Mature Oocytes of *Drosophila Melanogaster* to the Induction of Dominant Lethals Following Treatment of Mono- and Polyfunctional Aziridine Analogues. Mutat. Res., 14:250-253, 1972.

[66] Lueers, H., and G. Obe. Possible Mutagenic Activity of *p*-Benzoquinone. Mutat. Res., 15:77-80, 1972.

Benzoyl Peroxide

Benzoyl peroxide (CAS No. 94-36-0) was extensively tested in mice and rats between 1962 and 1967 by 6 authors on more than 1,100 animals [5]. Benzoyl peroxide is on the NIOSH Suspected Carcinogen List because in one of these studies, 1/30 mice developed a squamous papilloma after application of benzoyl peroxide in benzene to the skin. No recent mutagen or carcinogen references could be found on TOXLINE or CANCERLINE. It has been found negative in a dominant lethal mouse test, on an *E. coli* (pol A) mutagen test, and a *Micrococcus pyogenes* test [32]. There is very little doubt that benzoyl peroxide should be considered a noncarcinogen.

Benzyl Chloride

Benzyl chloride (α-chlorotoluene, CAS No. 100-44-7) has been found positive on a differential growth *E. coli* (pol A) mutagen test [46]. It is also positive on a subcutaneous rat test at 2.1 g/kg (51 weeks) in 3/14 rats and at 3.9 g/kg in 6/8 rats [67]. It is weakly mutagenic in *S. typhimurium* tests at 2 mg/plate [68], and is considered carcinogenic in rats by the IARC [67]. It is considered a probable carcinogen for this project.

Production and Persistence

In 1972 it was estimated that 3.6×10^7 kg was produced with 65-70% of this going towards the manufacture of butyl phthalate and 30-35% towards other organic products [67]. Production has been estimated at 4.5, 3.2 and 4.1×10^7 kg in 1974, 1975 and 1976 and is predicted to grow at 5-7% per year through 1980 [32]. It has a boiling point of 179°C and vapor pressure of 1 mm at 22°C [33].

---

[67] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976.

[68] McCann, J., et al. Detection of Carcinogens as Mutagens: Bacterial Tester Strains with R Factor Plasmids. Proc. Nat. Acad. Sci (USA), 72:979-983, 1975.

Biphenyl

There is one reference which shows subcutaneous biphenyl (diphenyl, CAS No. 92-52-4) to induce an excess of tumors in mice [69]. No supporting references could be found in CANCERLINE or TOXLINE. Biphenyl is therefore placed on the possible carcinogen list for this project.

Production and Persistence

It is estimated that 9.2×10^4 kg biphenyl is emitted per year from the manufacture of polychlorinated biphenyls [1]. Since the production of polychlorinated biphenyls has been stopped, this source of biphenyl emissions has probably ceased to exist. It has a boiling point of 254°C [33].

---

[69] Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume I. National Technical Information Service No. PB 223 159, 1968.

Bis(chloromethyl) Ether

Bis(chloromethyl) ether (BCME, dichloromethyl ether; CAS No. 542-88-1) is carcinogenic to mice following inhalation, skin application and subcutaneous administration [70]. It is also carcinogenic to rats by inhalation and subcutaneous administration [70]. Epidemiological data suggest it is also a human carcinogen [70]. It is being regulated as a carcinogen and will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that less than 100 kg BCME is emitted per year [1]. A primary source of emissions is the production of polymethylene polyphenyl isocyanate [1]. Its production in 1974 was estimated to be less than 450 kg [8]. In water the half-life of BCME is 38 seconds and in the air (50% relative humidity) its half-life is 25 minutes [8]. It has a boiling point of 104°C [8].

---

[70] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 231-238.

Butadiene

1,3-Butadiene (CAS No. 106-99-0) has not been extensively tested for mutagenicity or carcinogenicity. No references could be found on TOXLINE, CANCERLINE, or in the seven collected volumes of Reference 5 on tests conducted, although there is interest in a possible relationship between styrene-butadiene rubber plants and neoplasms of the lymphatic and hematopoietic tissue [71]. Butadiene will be considered a probable noncarcinogen for this project.

---

[71] Smith, A. H., and L. Ellis. Styrene Butadiene Rubber Synthetic Plants and Leukemia (Letter to Editor). J. Occup. Med., 19(7):441, 1977.

Captan

Captan has been found to be a potent mutagen, in both prokaryote and eukaryote test systems too numerous to list. It has also been found to produce hepatomas in mice [69]. Because of the many positive mutagenicity tests along with a marginally positive mouse carcinogenicity test, captan has been placed on the probable carcinogen list.

Production and Persistence

It is estimated that less than 100 kg per year of captan is emitted [1]. (Another estimate is production of 8.1×10^6 kg per year with 0.01 released, or 8×10^4 kg per year emitted [6].)

Carbon Disulfide

There is nothing in TOXLINE or CANCERLINE to indicate that carbon disulfide is a carcinogen or a mutagen. One industrial epidemiological study showed carbon disulfide to have no correlation with incidence of cancer [72].

---

[72] DiVito, G., and G. L. Sommi. The Incidence of Infectious Diseases, Hemopathies, and Neoplasms in Workers Exposed to Carbon Disulfide. Folia Med. (Napoli), 46(11):972-979, 1963.

Carbon Tetrachloride

Carbon tetrachloride (tetrachloromethane, CAS No. 56-23-5) has been reported to produce liver tumors in the mouse, hamster, and rat following administration by inhalation and oral ingestion [73]. It was not a mutagen as tested by several microbial systems [32]. Carbon tetrachloride is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1.2×10^7 kg of carbon tetrachloride is emitted per year [1]. Another estimate is a production of 4.5×10^8 kg with 2.7×10^7 kg released [7]. A document is available on the air pollution assessment of carbon tetrachloride [74]. Estimates of carbon tetrachloride production include 4.5×10^8 kg (1970) [73], 4.8×10^8 kg [6], 7.3×10^8 kg (1974) [8] and 5.3, 4.1, and 3.8×10^8 kg for 1974, 1975, and 1976 [32]. It is forecast that the 1975-1976 decline will continue. The half-life of carbon tetrachloride in the water is about 70,000 years [7], and in the troposphere it is about 10 years [8]. It is estimated to have a half-life of 10-33 weeks toward atmospheric photodegradation [74]. The boiling point of carbon tetrachloride is 76.7°C, and it has a vapor pressure of 90 mm at 20°C [33]. For a review of its production, uses and biological activity, see the Fishbein article [75].

---

[73] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 53-60.

[74] Johns, R. Air Pollution Assessment of Carbon Tetrachloride. National Technical Information Service No. PB 256 732, 1976.

[75] Fishbein, L. Industrial Mutagens and Potential Mutagens, I. Halogenated Aliphatic Derivatives. Mutat. Res., 32:267-308, 1976.

Chloracetic Acid

Chloracetic acid (monochloroacetic acid, CAS No. 79-11-8) has been reported as being carcinogenic in mice when injected subcutaneously at 100 mg/kg [2]. The primary reference, however, does not report a statistical difference in tumors; data reported for the test mice are not much different from those for the control mice [69]. In other tests, chloracetic acid was negative when given to 6 rats as 0.005-0.1% of their diet for 208 days [76] and negative when given at 46.4 mg/kg in the water of 72 mice for days 7-28 followed by 149 ppm in their diet for another 17 months [77]. It has also been found nonmutagenic by *B. subtilis* [78] and *S. typhimurium* [78-81] tests *in vitro*. All of these demonstrate that chloracetic acid is not a mutagen nor a carcinogen.

---

[76] Fuhrman, F. A., et al. Arch. Inst. Pharmacodym., 102:113-125, 1955.

[77] Innes, J. R. M., et al. J. Nat. Cancer Inst., 42:1101-1114, 1969.

[78] Elmore, J. D., et al. Vinyl Chloride Mutagenicity via the Metabolites Chlorooxirane and Chloroacetaldehyde Monomer Hydrate. Biochem. Biophys. Acta, 442:409-419, 1976.

[79] Rannug, U., et al. The Mutagenicity of Chloroethylene Oxide, Chloroacetaldehyde, 2-Chloroethanol and Chloroacetic Acid, Conceivable Metabolites of Vinyl Chloride. Chem. Biol. Interact., 12(3-4):251-263, 1976.

[80] Bartsch, H., et al. Human, Rat and Mouse-Liver Mediated Mutagenicity of Vinyl Chloride in *S. Typhimurium* Strains. Int. J. Cancer, 15(3):429-437, 1975.

[81] Malaveille, C., et al. Mutagenicity of Vinyl Chloride, Chloroethyleneoxide, Chloroacetaldehyde and Chloroethanol. Biochem. Biophys. Res. Comm., 63(2):363-370, 1975.

Chlordane

Chlordane has been found to be a carcinogen to mice in a study conducted by the National Cancer Institute [82]. It is also a mutagen in tests like the enhancement of viral transformation (personal communication with B. C. Casto on 9 February 1978). It is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1.1 x 10^7 kg per year of chlordane is produced [6].

---

[82] Bioassay of Chlordane for Possible Carcinogenicity (CAS No. 57-74-9. National Technical Information Service No. PB 271 977.

Cresols

Cresols (primarily *o*-cresol) have been shown to be promoters of carcinogenicity when given with initiators such as 3,4-benzpyrene (Kaiser), dimethylbenzanthracene [83] or in complex mixtures [84, 85]. On the other hand, normal adults excrete about 30 mg of volatile phenols per day of which 90% is *p*-cresol [86]. Thus, cresols are probably not carcinogens but could be promoters.

---

[83] Bakke, O. M., and T. Midtvedt. Influence of Germ-Free Status on the Excretion of Simple Phenols of Possible Significance in Tumor Promotion. Experimentia, 26(5):519, 1970.

[84] Bock, F. G., et al. Composition Studies on Tobacco. XLIV. Tumor-Promoting Activity of Subfractions of the Weak Acid Fraction of Cigarette Smoking Condensate. J. Nat. Cancer Inst., 47(2):429-436, 1971.

[85] Shustova, M. N., and L. N. Samiolovich. Blastomogenicity of Neutralized Soots from the Sulfate Shop of a Coke Plant. Gig. Sanit., 36(7):103-104, 1971.

[86] Bone, E. S., et al. The Production of Urinary Phenols by Human Gut Bacteria, (Meeting Abstract). J. Med. Microbiol., 9(2):vi, 1976.

Chlorobenzilate

Chlorobenzilate (CAS No. 510-15-6) has been found to produce hepatomas in mice when administered orally [69,77,87] and is listed by the U.S. Commission on Pesticides and Their Relationship to Environmental Health as a group B chemical (positive results in one or more animal species at 0.01 significance level [88]). Several short-term tests have been negative for chlorobenzilate [18]. For this project, it is considered a probable carcinogen.

Production and Persistence

A 1976 reference [6] cites a production of 9×10^5 kg per year, and it is said [87] that the 1971 production was 1×10^6 kg.

---

[87] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 75-81.

[88] Jurek, A. Carcinogenicity of Pesticides. Roczn. Panstw. Zakl. Hig., 25(5):563-576, 1974.

Chloroform

Some of the current literature [89-92] indicates that chloroform is a carcinogen. Even though more data are required before a final determination is made, the positive data on mice and rats suggest that chloroform be placed on the probable carcinogen list for this project.

Production and Persistence

It is estimated that 1 x 10^6 kg chloroform is emitted per year [1]. Another estimate is 1.7 x 10^7 kg per year [60] emitted. Production estimates are 1.3 x 10^8 kg per year [8], 1.1 x 10^8 [6], and 1.1 x 10^8 kg per year [89]. About 96% of production is converted to chlorodifluoromethane. In the troposphere chloroform degrades slowly with a 10-year half-life [8]. It reacts with HO radical with a $t_{1/2}$ of 13 hours [8] and hydrolyzes with a $t_{1/2}$ of 3,000 years [8,60]. The log partition coefficient is 1.97 for chloroform [60]. It has a vapor pressure of 160 mm at 20°C and a boiling point of 62°C [33]. It takes only 18-25 minutes to evaporate 50% of the chloroform from a 1-ppm solution at 25°C [33].

---

[89] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 61-65.

[90] Powers, M. B., and R. W. Yoelker. Evaluation of the Oncogenic Potential of Chloroform by Long-Term Oral Administration in Rodents (Meeting Abstract). Toxicol. Appl. Pharmacol., 37:179, 1976.

[91] Renne, R. A., et al. Pathology of Long-Term Oral Administration of Chloroform in Rodents (Meeting Abstract). Toxocol. Appl. Pharmacol., 37:179-180, 1976.

[92] Chloroform Tagged as Carcinogen in Mice. Chem. Eng. News, 54:6, 1976.

Chloroprene

Chloroprene (2-chloro-1,3-butadiene, CAS No. 126-99-8) although known to be toxic was not considered to be a suspected carcinogen until three Russian papers linked occupational exposure of chloroprene to skin and lung cancers [93-95]. Since that time, a short-term viral enhancement [96] test at 125 μg/ml (personal communication with B. C. Casto on 9 February 1978) and *S. typhimurium* (Ames) tests [97] have been positive, while long-term rat and mouse studies have been negative [98,99]. A review of health records and death certificates for DuPont Corporation employees exposed to chloroprene convinced investigators that no excess of any disease similar to that seen for vinyl chloride had been observed [100]. However, some increase in lung cancer has been seen this population [100]. Chloroprene has also been found to accelerate the growth of transplanted Crocker murine sarcoma in the rat [44]. Thus, it lies on the border between a possible and a probable carcinogen. It will be classified as a possible carcinogen for this project.

Production and Persistence

It is estimated that 7.5 x 10^6 kg chloroprene is emitted per year [1]. Another estimate is 2.7 x 10^6 kg/year released [44]. Some estimates of production are about 1.8 x 10^8 kg/year [6,44], 1.6 x 10^8 kg/year [8], and 1.8 x 10^8 kg and 1.6 x 10^8 kg in 1974 and 1975, with 4% annual growth predicted through 1981 [32]. Because of its low solubility and high volatility, it will soon migrate to the atmosphere [8]. In the atmosphere it is said to have an atmospheric half-life of less than 10 hours because of OH radical reaction [8]. Its boiling point is 59.4°C and it has a vapor pressure of 200 mm at 20°C [33].

---

[93] Khachatryan, E. A. The Role of Chloroprene in the Process of Skin Neoplasm Formation. Gig. Tr. Prof. Zabol., 16:54-55, 1972.

[94] Khachatryan, E. A. The Occurrence of Lung Cancer Among People Working with Chloroprene. Problems in Oncology, 18:85, 1972.

[95] Khachatryan, E. A. Lung Cancer Incidence Among Chloroprene Handling Workers. Yopr. Onkol., 18:85-86, 1972.

[96] Casto, B. C., et al. Assay of Industrial Chemicals in Syrian Hamster Cells for Enhancement of Viral Transformation. Proc. Am. Assoc. Cancer Res., 18:155, 1977.

[97] Bartsch, H., et al. The Predictive Value of Tissues-Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals. IARC Sci. Pub. No. 12, 1976. pp. 467-491.

[98] Zilfyan, V. N., et al. Experimental Study of Chloroprene for Carcinogenicity. Yopr. Onkol., 23:61-65, 1977.

[99] Zilfyan, V. N., et al. Results of a Study of Chloroprene for Carcinogenicity. Zh. Eksp. Klin. Med., 15:54-57, 1975.

[100] Lloyd, J. W. Cancer Risks Among Workers Exposed to Chloroprene. Ann. N.Y. Acad. Sci., 271:91-93, 1976.

Chloropropane

No reference to carcinogenic or mutagenic action of chloropropane could be found in TOXLINE, CANCERLINE, or any of the other references consulted. It is probably a noncarcinogen and will be considered as such for this project.

Chrysene

Chrysene [benzo(a)phenanthrene, CAS No. 218-01-9] is fairly well established as a weak carcinogen. It has produced skin tumors in mice following repeated painting, and 2-20 mg injected subcutaneously in mice produced tumors after a long induction period [101]. It is also a mutagen causing 167 revertants per microgram [52]. It is considered a probable carcinogen for this project.

Production and Persistence

Although chrysene is not a manufactured chemical, it is a product of combustion found widely dispersed in the environment. In one test of automobile exhaust, 12 μg was found after 1 minute of operation [101]. In the atmosphere, 150-490 μg chrysene has been found per gram organic particulate matter [101]. It has a boiling point of 488°C [33].

---

[101] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3, 1973. pp. 159-177.

Cumene Hydroperoxide

Cumene hydroperoxide (dimethylbenzyl hydroperoxide) is cited as being a carcinogen but at 34 and 90 mg/kg did not induce satistically significant dominant lethal effects in mice [30, 102]. Cumene hydroperoxide is said to cause neoplasms in mice both by inhalation at 304 mg/kg [103] and subcutaneously at 10 g/kg [104]. On the basis of the two animal studies, it is considered a possible carcinogen for this project.

Production and Persistence

It is estimated [8] that the 1974 production was 1.4 x 10^9 kg. Another estimate of production [6] is 9.1 x 10^8 kg per year with a production loss factor of 0.015, or 1.3 x 10^7 kg/year. It has a vapor pressure of 1 mm at 70°C [6]. Because of its low volatility and moderate solubility in water, it is not likely to remain in the atmosphere [8]. Photochemical and HO radical reactions are likely pathways for transformation of peroxides in the atmosphere with a half-life of less than a few hours [8].

---

[102] Epstein, S. S., and H. Shafner. Chemical Mutagens in the Human Environment. Nature, 219:385-387, 1968.

[103] Radiation Research, Supplement 3:193, 1963 (as cited in Reference 2).

[104] J. Nat. Cancer Inst., 37:825, 1966 (as cited in Reference 2).

DDT

DDT [1,1,1-trichloro-2,2-di-(4-chlorophenyl) ethane, CAS No. 50-29-3] has both positive and negative *in vivo* and *in vitro* data. It was negative in feeding studies of dogs and monkeys [105] and in a differential growth *E. coli* (pol A) mutagen test [46]. Given orally, it produced liver cell tumors in several strains of mice, and some of its metabolites produced lung tumors in mice [46]. It is positive in a recessive lethal *Drosophila* test [106]. All things considered, it is probably a carcinogen and will be classified as one for this project.

Production and Persistence

In 1971, 2×10^7 kg was the estimated production [105]. In 1971 it was found in the air in concentrations of 0.1 ng/m^3 to 1.56 μg/m^3. The soil half-life is estimated to be 15 years [105]. It has a vapor pressure of 1.9×10^{-7} mm at 20°C and a melting point of 74°C.

---

[105] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 83-124.

[106] Vogel, E. The Relation Between Mutational Pattern and Concentration by Chemical Mutagens in *Drosophila*. IARC Sci. Pub. No. 12, 1976. pp. 117-137.

Di-tert-butyl Peroxide

Di-tert-butyl peroxide [bis(1,1-dimethylethyl) peroxide, CAS No 110-05-4] has been found to induce malignant lymphomas in 7/35 mice which inhaled 100 μg/m^3 of this chemical [107]. (Tert-butyl hydroperoxide has also been found negative by skin application tests on mice [109, 110].) Di-tert-butyl peroxide is on a list of "suspected carcinogens" studied for environmental fate [8]. Since the positive mice test results were by the inhalation route, which has fewer false positives than does injection, di-tert-butyl peroxide will be considered a possible carcinogen for this project. Considering the type and date (1963) of the positive tests, however, negative short-term *in vitro* mutagenicity data would probably change its classification to a probable non-carcinogen by the criteria used for this project.

Production and Persistence

Production is estimated to be 3 million pounds per year [8]. It is only slightly volatile but moderately soluble in water. Thus most of the di-tert-butyl peroxide will remain in the water system. In the water the presence of >1 ppm Fe^{2+} and Mn^{2+} leads to decomposition to acids and alcohols with $t_{1/2}$ <10 hours [8]. In the atmosphere photochemical and HO radical decomposition leads to a $t_{1/2}$ of 79 hours [8].

---

[107] Kotin, P., and H. L. Falk. Radiation Research Supplement 3:193-211, 1963 (as cited in Reference 5).

[108] Saffioti, U., and P. Shubik. Nat. Cancer Inst. Monog., 10:489-507, 1963 (as cited in Reference 5).

[109] Hoshing, H., et al. Gann 61(2):121-124, 1970 (as cited in Reference 5).

[110] Van Duuren, B. L., et al. J. Nat. Cancer Inst., 39:1217-1228, 1967 (as cited in Reference 5).

Di(2-ethylhexyl) Phthalate

Di(2-ethylhexyl) phthalate (DEHP, dioctyl phthalate, DOP; CAS No. 117-81-7) is a high-volume plasticizer which had in the past been considered virtually nontoxic as judged by various acute and chronic tests [111]. Although early animal tests (dog, guinea pig, rat) were negative [112], at least one source [6] now cites neoplastic effects in rats orally given 43.2 g/kg (96 weeks) di(2-ethylhexyl) phthalate. Although this dose is rather high, there are also several references which show this chemical to be both mutagenic and teratogenic [113-121]. It is therefore classed as a possible carcinogen for this project, at least until a carcinogen bioassay being conducted under NCI contract [122] is concluded and reported.

Production and Persistence

It is estimated that 2.6×10^5 kg DEHP is emitted per year from stationary sources [1]. Other estimates are 2.0×10^8 kg produced and released [60] and 1.8×10^8 kg produced in 1974 [6]. It is said to biodegrade rapidly in water and sludge [123].

In the air it reacts with the HO radical with a half-life of 1 day [60]. It has a boiling point of 385°C and a vapor pressure of 1.2 mm at 200°C [33].

---

[111] Documentation of the Threshold Limit Values for Substances in Workroom Air. American Conference of Governmental Industrial Hygienists, 1976. pp. 96-97.

[112] Shubik, P., et al. Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Supplement I. National Technical Information Service No. PB 216 248, 1957.

[113] Singh, A. R., et al. Mutagenic and Antifertility Sensitivities of Mice to Di-2-ethylhexyl Phthalate (DEHP) and Dimethoxyethyl Phthalate (DMEP). Toxicol. Appl. Pharmacol., 29(1):35-46, 1974.

[114] Mathur, S. P. Respirometric Evidence of the Utilization of Dioctyl and Di-2-ethylhexyl Phthalate Plasticizers. J. Environ. Qual., 3(3):207-209, 1974.

[115] Peakall, D. B. Phthalate Esters: Occurrence and Biological Effects. Residue Reviews, 54:1-41, 1975 (177 references).

[116] Recent Progress in Safety Evaluation Studies on Plasticizers and Plastics and Their Controlled Use in Japan. Environ. Health Perspec., 17:203-209, 1976.

[117] Singh, A. R., et al. Mutagenic and Antifertility Sensitivities of Mice to Phthalic-Acid Esters. J. Anim. Sci., 38(1):216, 1974.

[118] Taylor, B. F., and E. F. Corcoran. Biodegradation of Phthalic Acids and Esters. Contract ES-00994-02, National Institute of Environmental Health Sciences, 1975.

[119] Autain, J. Toxicity and Health Threats of Phthalate Esters, Review of the Literature. Environ. Health Perspec., 4:3-26, 1973.

[120] Yagi, Y., et al. Teratogenicity and Mutagenicity of a Phthalate Ester. Teratology, 14:259-260, 1976.

[121] Dillingham, E. O., and J. Autain. Teratogenicity, Mutagenicity and Cellular Toxicity of Phthalate Esters. Environ. Health Perspec. 3:81-89, 1973.

[122] Landon, J. C. Carcinogenesis Bioassay of Di(2-ethylhexyl) Phthalate. National Cancer Institute contract with Tracor Jitco, Inc., 10/76-9/77, 1977.

[123] Saeger, V. W., and E. S. Tucker. Biodegradation of Phthalic Acid Esters in River Water and Activated Sludges. Appl. Environ. Microbiol., 31(1):29-34, 1976.

2,4-Diaminoanisole

2,4-Diaminoanisole (4-methoxy-*m*-phenylenediamine) was nonmutagenic in the L51178Y mouse lymphoma cell test [124] and negative on rat skin [125] (in combination with other chemicals) and mouse skin [126] (the sulfate form) carcinogen tests. It did not produce dominant lethal mutations in rats [127].

It has been shown to be mutagenic in *S. typhimurium* [128-130], usually with S-9 activation. It also induced sex-linked recessive lethal mutations in *Drosophila melanogaster* [131] (sulfate form) with peak activity in the active germ cells (spermatids and spermatocytes). Preliminary results from an NCI study indicate that rats and mice fed this chemical (0.12% to 0.24%) had an excess of site-specific (thyroid and skin) malignant tumors [133]. Also, two epidemiologic studies suggest excess cancer among cosmetologists [132]. Diaminoanisole is on the NIOSH Safety Alert list for its carcinogenic potential [133] and will be considered a probable carcinogen for this project.

Production and Persistence

NIOSH is unaware of any current domestic production but reports that on the order of 25,000 pounds per year are imported [133].

---

[124] Palmer, K. A., et al. The Mutagenic Assay of Some Hair Dye Components Using the Thymidine Kinane Locus of L51178Y Mouse Lymphoma Cells (Meeting Abstract). Toxicol. Appl. Pharmacol., 37(1):108, 1976.

[125] Kinkel, H. J., and S. Holzmann. Study of Long-Term Percutaneous Toxicity and Carcinogenicity of Hair Dyes (Oxidizing Dyes) in Rats. Food Cosmet. Toxicol., 11(4):641-648, 1973.

[126] Burnett, C., et al. Long-Term Toxicity Studies on Oxidation Hair Dyes. Food Cosmet. Toxicol., 13(3):353-357, 1975.

[127] Burnett, C., et al. Dominant Lethal Mutagenicity Study on Hair Dyes. J. Toxicol. Environ. Health, 2(3):657-662, 1977.

[128] Dybing, E., and S. S. Thorgeirsson. Metabolic Activation of 2,3-Diaminoanisole, a Hair-Dye Component. Biochem. Pharmacol., 26(8):729-734, 1977.

[129] Dybing, E., and T. Aune. Hexachlorobenzene Induction of 2,4-Diaminanisole Mutagenicity *in Vitro*. Acta Pharmacol. Toxicol., 40(5):575-583, 1977 (24 references).

[130] Ames. B. N., et al. Hair Dyes are Mutagenic; Identification of a Variety of Mutagenic Ingredients. Proc. Natl. Acad. Sci. (USA) 72(6):2423-2427, 1975.

[131] Blijleven, W. G. Mutagenicity of Four Hair Dyes in *Drosphila Melanogaster*. Mutat. Res., 48(2):181-185, 1977.

[132] Health Hazards; 2,4-Diaminoanisole. Occupational Safety & Health Reporter, 7(35):1331, 1978.

[133] 2,4-Diaminoanisole (4-Methoxy-*m*-phenylenediamine) in Hair and Fur Dyes. Current Intelligence Bulletin 19, January 13, 1978.

Diazinon

Diazinon has been reported to be slightly teratogenic in rats when given on the 11th day of gestation [134]. An increase in chromatid breaks has been noted in the lymphocytes of humans after ingestion of phosphate insecticides including diazinon [135] and in cultivated human lymphocytes [136].

On the other hand, diazinon has been found to be nonmutagenic in *S. typhimurium* mutation tests [137].

Diazinon also does not cause mutations in the 5-MT *E. coli* test [138], the WP2 TRY - to prototrophy *E. coli* test [139], two other *E. coli* tests [18], or a *S. cerevisiae* mitotic gene conversion test [18].

The majority of the information indicates that diazinon is probably not a carcinogen.

---

[134] Kimbrough, R. D., and T. B. Gaines. Effect of Organic Phosphorous Compounds and Alkylating Agents on the Rat Fetus. Arch. Environ. Health, 16:805-808, 1968.

[135] Trinh-Van-Bao, et al. Chromosome Aberrations in Patients Suffering Acute Organic Phosphate Insecticide Intoxication. Humangenetik, 24:33-57, 1974.

[136] Tzoneva-Maneva, M. T., et al. Influence of Diazinon and Lindane on the Mitotic Activity and the Caryotype of Human Lymphocytes, Cultivated *in Vitro*. Bibl. Haematol. (Base 1), 38(1):344-347, 1971.

[137] Marshall, T. C., et al. Screening of Pesticides for Mutagenic Potential Using *Salmonella Typhimurium* Mutants. J. Agric. Food Chem., 24:560-563, 1976.

[138] Mohn, G. 5-Methyltryptophan Resistance Mutations in *Escherichia Coli* K-12. Mutat. Res., 20(1):7-15, 1973.

[139] Ashwood-Smith, M. J., et al. Mutagenicity of Dichlorvos. Nature, 240:418-419, 1972.

o-Dichlorobenzene

A negative animal study of *o*-dichlorobenzene (CAS No. 95-50-1) has been conducted [5], but it was a short-term (<6 months) study which would not be expected to show carcinogenicity. A few positive case studies have been reported, but with insufficient supporting evidence to show cause and effect [140]. A few *in vitro* tests have been conducted [141-143]. In *Aspergillus nidulans*, 200 mg/ml for 60 minutes causes an increase in reversion to methionine prototrophy from 3 x 10^6 to 5 x 10^6 reversions [32]. It was negative in a *S. typhimurium* spot test at 1-5 µl in eigth strains[32]. Because of the limited positive test data on systems which have not been extensively evaluated, *o*-dichlorobenzene will be considered a probable noncarcinogen (with some significant positive data) for this project.

---

[140] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 231-244.

[141] Guerin, M., et al. Inhibitory Action of Chemical Carcinogens on Mitosis of Rat Lung Cell Cultures; 2. Comparative Study of Carcinogenic and Noncarcinogenic Substances. C. R. Soc. Biol., 165:2255-2258, 1971.

[142] Prasad, I. Mutagenic Effects of the Herbicide 3',4'-Dichloro-propionanilide and Its Degradation Products. Can. J. Microbiol., 16:369-372, 1970.

[143] Prasad, I., and D. Pramer. Mutagenic Activity of Some Chloroanilines and Chlorobenzenes. Genetics, 60:212-213, 1968.

p-Dichlorobenzene

Many negative animal studies of *p*-dichlorobenzene (CAS No. 106-46-7) have been conducted [5], but all of them have been short-term (<9 months) studies which would not be expected to show carcinogenicity. A few positive case studies have been reported but with insufficient supporting evidence to show cause and effect [140]. A few *in vitro* tests have been conducted [141-143]. It is reported that *p*-dichlorobenzene is a mutagen to higher plants and causes chromosomal breaks [56]. In *Aspergillus nidulans*, 200 mg/ml for 60 minutes causes an increase in reversion to methionine prototrophy from 3×10^6 to 11×10^6 reversions [32]. Because of the limited positive test data on systems which have not been extensively evaluated, *p*-dichlorobenzene will be considered a probable noncarcinogen with some significant positive data) for this project.

Dichlorobenzidine

3,3'-Dichlorobenzidine (CAS No. 91-94-1) has been found to be carcinogenic in the rat following oral and subcutaneous administration and in the hamster after oral administration [144, 145]. Many other positive responses are noted in TOXLINE and CANCERLINE, and it is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 2.1×10^6 kg is produced per year with 4.5×10^3 kg per year released [60]. Other estimates of production are 1.6×10^6 kg in 1971 [144] and 2.1×10^6 kg per year [6]. Dichlorobenzidine is somewhat reactive towards RO_2 ($t_{1/2}$ = 40 days) and very reactive towards HO and O_3 ($t_{1/2}$ = 1 day) [60]. Its melting point is 133°C [144].

---

[144] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 49-55.

[145] Stula, E. F., et al. Experimental Neoplasia in Rats from Oral Administration of 3,3-Dichlorobenzidine, 4,4'-Methylene bis(2-chloroaniline), and 4,4'-Methylene bis(2-methylaniline). Toxicol. Appl. Pharmacol., 31(1):159-176, 1975.

Dichlorobutene

1,4-Dichlorobutene-2 is a mutagen of *S. typhimurium* with microsomes enhancing the effect [146]. 3,4-Dichlorobutene-1 is also a mutagen in that system with or without nicotinamide adenine dinucleotide phosphate (NADP), giving 490 reverts/μmole with NADP and 345 reverts/μmole without NADP [146]. *Trans*-1,4-dichlorobutene-2 has been found to be a weak carcinogen to ICR/HA Swiss mice when given by subcutaneous injection or by intraperitoneal injection but not by skin application [147]. It was found not to be a tumor initiator in a two-stage test [147]. Because of the carcinogenic and mutagenic data, it has been placed on the probable carcinogen list for this project.

Production and Persistence

It is estimated that 8.7 x 10^5 kg is emitted per year in the manufacture of polychloroprene [1]. 1,4-Dichlorobutene has a boiling point of 158°C [33].

---

[146] Bartsch, H., et al. Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissues. Proc. Am. Assoc. Cancer Res., 17:17, 1976.

[147] Van Duuren, B. L., et al. Carcinogenic Activity of Di- and Tri-functional α-Chloro Ethers and of 1,4-Dichlorobutene-2 in ICR/HA Swiss Mice. Cancer Res., 35:2553-2557, 1975.

Dichlorodifluoromethane

Dichlorodifluoromethane (Freon-12) has been shown to be nonmutagenic in *S. typhimurium* tests [148] but may cause some (mutagenic?) changes in conidia formation in *Neurospora crassa* [149]. More information is needed on the mutagenic and carcinogenic potential of Freons. No other information could be found on CANCERLINE or TOXLINE. At the present time, it appears as if Freons are noncarcinogens.

---

[148] Andrews, A. W., et al. The Identification of Endogeneous and Exogeneous Mutagenic Compounds. 4th Carcinogenesis Bioassay Program, Orlando, Florida, February 1976.

[149] Stevens, S., et al. Phenotypic and Genetic Effects in *Neurospora Crassa* Produced by Selected Gases and Gases Mixed with Oxygen. Develop. Ind. Microbiol., 12:346-353, 1971.

1,1-Dichloroethane

The primary reference [150] cited for 1,1-dichloroethane (CAS No. 75-34-3) in the NIOSH Suspected Carcinogen list shows very minor teratogenic effects even at the highest concentration used (6,000 ppm). Although there are many references to 1,2-dichloroethane, TOXLINE and CANCERLINE provided no significant references on the mutagenicity or carcinogenicity of 1,1-dichloroethane. A recent report from the National Cancer Institute [151] disclosed findings indicative of a possible carcinogenic potential for this compound but could supply no conclusive evidence. Investigators found dose-related marginal increases in mammary adenocarcinomas and in hemangiosarcomas among female rats and a statistically significant increase in the incidence of endometrial stromal polyps among dosed female mice. For this project 1,1-dichloroethane will be classified as a possible carcinogen.

Production and Persistence

It is estimated that 2.6 x 10^6 kg of dichloroethane is emitted per year from stationary sources [1]. Half of the 1,1-dichloroethane will evaporate from a 1-ppm water solution at 25°C in 22 minutes [33]. It has a boiling point of 57.3°C and a vapor pressure of 180 mm at 20°C [33].

---

[150] Schwetz, B. A., et al. Embryo- and Fetotoxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane, and Methyl Ethyl Ketone in Rats. Toxicol. Appl. Pharmacol., 28:452-464, 1974.

[151] National Cancer Institute Draft Summaries of Bioassay Reports, 1,1-Dichloroethane. Chem. Reg. Rep., 1(45):1597-1598, 1978.

Dichloronaphthoquinone

Dichloronaphthoquinone (Dichlone) did not cause point mutation in a microbial test system [152]. It has, however, been found to cause reticulum cell sarcomas (Type A) in 9/64 mice when injected subcutaneously in B6C3F1 or B6AKF1 strains of mice compared to 14/613 reticulum cell sarcomas for the subcutaneous controls [69]. This was significant at a 0.01 confidence level. Because of the limited number of mice involved, and the lack of other references on CANCERLINE and TOXLINE, dichloronaphthoquinone will be considered a possible carcinogen for this project.

Production and Persistence

It is estimated that 900 kg/year are emitted from stationary sources [1]. Dichloronaphthoquinone has a melting point of 193°C and a 7.84 vapor density [33].

---

[152] Anderson, K. J., et al. Evaluation of Herbicides for Possible Mutagenic Properties. J. Agr. Food Chem., 20:649-656, 1972.

Dichlorophenol

Nothing was found in CANCERLINE to indicate that dichlorophenol is a carcinogen or a mutagen. A 1959 reference [153] cited in the NIOSH Suspected Carcinogen list shows that 2,4-dichlorophenol may be a promoter or cocarcinogen when applied to the skin of mice in combination with benzene and dimethylbenzanthracene. Other than this reference, dichlorophenol is not listed in Reference 5. Because of the lack of data, dichlorophenol has been placed on the probable noncarcinogen list as a possible promoter.

---

[153] Boutwell, R. K., and D. K. Bosch. The Tumor-Promoting Action of Phenol and Related Compounds for Mouse Skin. Cancer Res., 19:413-424, 1959.

Dichloropropene

1,3-Dichloropropene at 1 ppm for 6 months has been shown to have no adverse effects [154]. Both *cis* and *trans* isomers are mutagenic to TA1535 and TA100 *S. typhimurium* strains without activation [31, 155, 156]. It will be considered a possible carcinogen for this project.

Production and Persistence

It is estimated that 6 x 10^7 pounds of a dichloropropane/dichloropropene mixture is manufactured a year [56]. Assuming 50% dichloropropene, 3 x 10^7 pounds is released a year. It is said to react with OH and O_3 with a $t_{½}$ = 3 days, and to have a $t_{½}$ = 7 days in water [56]. It has a boiling point of 104°C and 50% of a 1-ppm water solution will evaporate in 31 minutes [33].

---

[154] Torkelson, T. R., and F. Oyen. The Toxicity of 1,3-Dichloropropene as Determined by Repeated Exposure of Laboratory Animals. Am. Indust. Hyg. Assoc. J., 38(5):217, 1977.

[155] DeLorenzo, F., et al. Mutagenicity of Pesticides Containing 1,3-Dichloropropene. Cancer Res., 37(6):1915-1917, 1977.

[156] Neudecher, T., et al. *In Vitro* Mutagenicity of the Soil Nematicide 1,3-Dichloropropene. Experientia, 33(8):1084-1085, 1977.

Dichloropropionic Acid

Dichloropropionic acid (Dalapon) is a herbicide which has been found nonmutagenic in a *S. typhimurium* test [152]. No other significant data have been found, so it has been placed on the probable noncarcinogen list.

Dichlorovinyl Dimethyl Phosphate (Dichlorvos)

Dichlorovinyl dimethyl phosphate (DDP) has been shown to be mutagenic in many different short-term tests [18], including *S. typhimurium* tests [157], but has been shown to be noncarcinogenic by oral and inhalation studies in rats and mice [158]. Because of the mutagen studies, DDP is to be listed on the possible carcinogen list for this project.

Production and Persistence

It is estimated that 200 kg/year is emitted from stationary sources [1]. DDP has a boiling point of 120°C at 14 mm [33].

---

[157] Shirasu, Y., et al. Mutagenicity Screening of Pesticides in the Microbial System. Mutat. Res., 40:19-30, 1976.

[158] Bioassay of Dichlorvos for Possible Carcinogenicity, CAS No. 62-73-7. National Technical Information Service No. PB 270 937, 1977.

Dimethylacetamide

Dimethylacetamide was negative in a mitotic index test for epidermal hyperplasia [159]. It is cited in the NIOSH Registry of Toxic Effects of Chemical Substances as being teratogenic to rats after intraperitoneal (I.P.) injection. One reference was found in the Survey of Chemical Substances Which Have Been Tested for Carcinogenic Activity (1968-1969) in which rats were given the chemical intergastrically at 0.1 to 30 mg/d for 260 doses [160]. The tumors found do not appear to be related to dose. No other references could be found in CANCERLINE or TOXLINE which would suggest that dimethylacetamide is a mutagen or a carcinogen, so it will be classified as a probable noncarcinogen for this project.

---

[159] Rieger, M. M. Cosmetic Science: 1975 Literature Survey. Cosmet. Perfum., 91(4):25-36, 1976.

[160] Hadidian, Z., et al. J. Nat. Cancer Inst., 41(4):985-1036, 1968.

Dimethylamine

Dimethylamine (methanamine, N-methyl) has been reported to combine with nitrates or nitrites both *in vitro* and *in vivo* (by saliva or intestine flora) to form the carcinogen called dimethylnitrosamine or nitrosodimethylamine (more than 20 references in TOXLINE. Dimethylamine may also combine with ozone and nitrogen tetroxide in the atmosphere [161]. In TOXLINE and CANCERLINE there are 74 and 16 references, respectively, which deal with mutagenic or carcinogenic aspects of dimethylamine. These references, along with those in Chemical Abstracts, appear to indicate that although dimethylamine is a potent cocarcinogen, it is not by itself carcinogenic. For this project, it will be considered a noncarcinogen but will be considered when cofactors are evaluated.

---

[161] Dushutin, K. K., and E. D. Sopach. The Role of the Reaction of Dimethylamine with Nitrogen Tetroxide and Ozone in Atmospheric Pollution. Gig. Sanit., 7:14-18, 1976.

Dimethylhydrazine

1,1-Dimethylhydrazine (CAS No. 57-14-7) has been found to be carcinogenic in mice after oral administration [162]. It also causes tumors of the colon in rats (but not swine, dogs, or guinea pigs - perhaps because of toxicity) fed 30 mg/kg dimethylhydrazine [163]. Many other positive references are found in TOXLINE and CANCERLINE, and it is considered a probable carcinogen for this project.

Production and Persistence

Production is estimated at $<5 \times 10^5$ kg in 1973 [6, 8, 162], with a 0.01 fraction of dispersion [6]. Since it is polar, nonvolatile, and soluble in water, there would not be a significant transfer to the atmosphere [8]. It reacts with oxidizing materials in the atmosphere [6] and has an expected half-life of 2.1 hours by reaction with the HO radical [8]. Dimethylhydrazine has a boiling point of 63.3°C and a vapor pressure of 157 mm at 25°C [6].

---

[162] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 137-143.

[163] Wilson, R. B. Species Variation in Response to Dimethylhydrazine. Toxicol. Appl. Pharmacol., 38(3):647-650, 1976.

Dinitrotoluene

2,4-Dinitrotoluene has been found by the National Cancer Institute to be noncarcinogenic to mice but carcinogenic to rats [164]. It has been placed on the probable carcinogen list for this project.

Production and Persistence

It is estimated that 400 kg dinitrotoluene is emitted per year from stationary sources [1]. It has a boiling point of 300°C [33].

---

[164] National Cancer Institute Draft Summaries of Bioassay Reports, 2,4-Dinitrotoluene. Chem. Reg. Rep., 1(45):1598, 1978.

Dioxane

1,4-Dioxane (CAS No. 123-91-1) has been shown to be carcinogenic to rats [165, 166] and guinea pigs [167] by oral administration. It produced malignant tumors of the nasal cavity and liver in rats and tumors of the liver and gall bladder in guinea pigs. It was also active as a promoter in a two-stage skin carcinogenesis study in mice but produced no carcinogenic effect in one inhalation study in rats [168]. For this project, it is considered a probable carcinogen.

Production and Persistence

The 1972 production has been estimated to be 6.3 x 10^6 kg [6, 44, 167] and the 1973 production to be 7.4 x 10^6 kg [167], with most of this being released to the environment [44]. In the atmosphere it reacts with the HO radical with a half-life of 9.6 hours [6, 44]. It has a boiling point of 101°C and a vapor pressure of 30 mm at 20°C and 37-39 mm at 25°C [6, 33, 167].

---

[165] Kociba, R. J., et al. 1,4-Dioxane: Correlation of the Results of Chronic Ingestion and Inhalation Studies with its Dose-Dependent Fate in Rats. Aerosp. Med. Res. Lab. (Tech. Rep.) AMRL-TR-125, 1975. pp. 345-354.

[166] Argus, M. F., et al. Dose-Response and Ultrastructural Alternatives in Dioxane Carcinogenesis. Eur. J. Cancer, 9(4):237-243, 1973.

[167] IARC Monographs: Evlauation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 247-256.

[168] Torkelson, T. R., et al. 1,4-Dioxane. II. 2-Year Inhalation Study in Rats. Toxicol. Appl. Pharmacol., 30(2): 287-298, 1974.

Diphenyl Oxide

No positive or negative data could be found for diphenyl oxide (phenyl ether, CAS No. 101-84-8) on TOXLINE, CANCERLINE, or in the Survey of Compounds Which Have Been Tested for Carcinogenic Activity (Volumes 1-7). It is, therefore, listed as a probable noncarcinogen for this project.

Disodium Methanearsonate

Disodium methanearsonate has been cited as being carcinogenic, but no further data are given in this reference [6]. It has been found to be nonmutagenic when tested with five strains of *S. typhimurium*, mitotic recombination of *S. cerevisiae*, and relative toxicity assays in *E. coli* and *B. subtilis* [169]. In all tests except the *B. subtilis*, the chemical was tested using the S-9 microsome activation. Methanearsonates have also been tested for mutagenesis by other authors [152, 157]. The lack of confirming data from TOXLINE or CANCERLINE and all indications other than the first reference demonstrate that this chemical is probably a noncarcinogen.

---

[169] Simmon, V. F., et al. *In Vitro* Mutagenic Studies of Twenty Pesticides. Toxicol. Appl. Pharmacol., 37(1):109, 1976.

Dursban

Dursban has been shown to be more toxic to the repair deficient strains of *B. subtilis* and *E. coli* than in repair proficient strains of these organisms. It was not, however, found to be a mutagen on *S. typhimurium* assays or on the mitotic recombination of *S. cerevisiae* [169]. It is considered a noncarcinogen for this project.

Endosulfan

Endosulfan has been found to marginally increase ($P = 0.05$) the total number of tumors and the pulmonary adenomas in mice given the compound orally [69]. Endosulfan has been found to be nonmutagenic in three different *E. coli* mutagen tests [18]. In a National Cancer Institute study [170], endosulfan was found to be noncarcinogenic to both mice and rats. Because of the limited amount of positive carcinogenic data and the many negative studies, endosulfan has been placed on the probable noncarcinogen list.

---

[170] National Cancer Institute Draft Summaries of Bioassay Reports. Chem. Reg. Rep., 1(45):1608-1609, 1978.

Endrin

Endrin (CAS No. 72-20-9) has been reported to cause chromosome breakage in cells [171]. Endrin was nonmutagenic by a *S. typhimurium* test using mouse liver microsomes [172] and has tested negative on several *E. coli* tests [18]. Rat feeding studies (up to 100 ppm) showed no increase in tumor incidence [173]. Endrin will be considered a probable noncarcinogen for this project.

---

[171] Grant, W. F. Cytological Effects of Environmental Mutagens-Pesticides. Mutat. Res., 21(4):221-222, 1973.

[172] Van Dijck, P., and H. Van de Voorde. Mutagenicity Versus Carcinogenicity of Organochloride Insecticides. Meded. Fac. Landbouwwet., Rijksuniv. Gent, 41(2, part 2):1491-1498, 1976.

[173] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 157-171.

Epichlorohydrin

Epichlorohydrin (chloromethyl oxirane, 1-chloro-2,3-epoxy-propane; CAS No. 106-89-8) has been reported to be carcinogenic in mice by subcutaneous injection and active as an initiator in a two-stage skin carcinogensis study in mice [174]. Epichlorohydrin is also a mutagen causing chromosome aberrations, mutating *S. typhimurium* in a host mediated assay and inducing reversions to prototrophy in *S. typhimurium*, *E. coli*, and *Neurospora crassa* [32]. It will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 2.2×10^5 kg is emitted per year [1]. Production in 1973 was estimated [8, 32, 174] to be 1.6×10^8 kg, 1.5×10^8 kg and 8.2×10^7 kg with a more recent estimate [6] of 2.2×10^8 kg. The production is expected to grow 4-5% a year [32]. In the atmosphere epoxides have a half-life of 3 to 11 hours [8]. Epichlorohydrin has a boiling point of 117°C and a vapor pressure of 12 mm at 20°C [33].

---

[174] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 131-139.

Eptam

Eptam (ethyl di-n-propylthiocarbamate, CAS No. 759-94-4) was negative in a bone marrow chromosomal aberration test when fed to rats at 1/5 LD_{50} (LD_{50} = 1,630 mg/kg) [175]. Eptam may have had an effect on *Vicia faba* [176]. It is cited as belonging to the C4 classification of pesticides [88] (negative, but in only one species of animal) but also referenced as being a neoplastic agent [6]. Neither of these primary references could be found on CANCERLINE, TOXLINE, MEDLINE, or in the entire collection of Reference 5. For this project it will be classified as a noncarcinogen.

---

[175] Kurinnyi, A. I. Mutagenic Activity of Some Pesticides Derivatives of Urea, Carbamic, and Thiocarbamic Acids. Tsitol. Genet., 11(4):357-359, 1977.

[176] Hakeek, H., and A. Shehab. Cytological Effects of Eptam and Cotoran on *Vicia Faba*. Egypt. J. Bot., 16(1-3):303-311, 1974.

Ethanol

Much has been written about the mutagenicity and carcinogenicity of ethanol [177] (87 references in TOXLINE) for both positive [178] and negative [179] results. It has been tested extensively in animal systems [5]. In general it is considered a noncarcinogen and nonmutagen and has been removed from the lastest NIOSH Suspected Carcinogens List. It will be considered a probable noncarcinogen for this project.

---

[177] Rydberg, U., and S. Skerfuing. The Toxicity of Ethanol: A Tentative Risk Evaluation. Adv. Exp. Med. Biol., 85B: 403-419, 1977 (57 references).

[178] Braun, R., and J. Schoeneick. Influences of Ethanol and Carbon Tetrachloride on the Mutagenic Effectivity of Cyclophosphamide in the Host-Mediated Assay with *Salmonella Typhimurium*. Mutat. Res., 31(3):191-194, 1975.

[179] Charbey, R. C., et al. Evaluation of the Effect of Ethanol on the Frequency of Micronuclei in the Bone Marrow of Swiss Mice. Mutat. Res., 43(3):441-444, 1977.

Ethylbenzene

No data have been found to indicate that ethylbenzene is a mutagen or a carcinogen. A review of its use as a fragrance is noted [180]. Ethylbenzene has been found noncarcinogenic to rats, guinea pigs, rabits and monkeys by inhalation and to rats orally [7]. It is negative on the viral enhancement of hamster cell transformation (personal communication from B. C. Casto on 9 February 1978). It is therefore classified as a noncarcinogen for this project.

---

[180] Opdyke, D. L. Monographs on Fragrance Raw Materials Ethylbenzene. Food Cosmet. Toxicol., 13(Suppl.):803-804, 1975.

Ethylene

No data were found to indicate that ethylene is a mutagen or a carcinogen. It is also a normal metabolite of the human body. It is therefore classified as a probable noncarcinogen for this project.

Ethylene Dibromide

Ethylene dibromide (1,2-dibromoethane, ethylene bromide; CAS No. 106-93-4) has been found to produce squamous-cell carcinomas of the forestomach in mice and rats after its oral administration [181]. It has also been reported to be mutagenic in *S. typhimurim, E. coli, Neurospora crassa, S. cerevisiae, Tradescantia, Serratia marcescens*, and *Drosophila melanogaster* test systems [32, 75, 182]. Ethylene dibromide will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 8.9×10^5 kg of ethylene dibromide is emitted per year from stationary sources [1]. Another reference cites a production of 1.43×10^8 kg with 1.38×10^8 kg released [7]. Other references cite production of 1.5×10^8 kg (1974) [8, 181], 1.4×10^8 kg [6], and 1.5×10^8 kg, 1.2×10^8 kg for 1974 and 1975 [32]. The use of ethylene dibromide in gasoline is predicted to drop by 10% a year through 1980, while its use as a fumigant may be terminated by EPA action in light of the above animal studies [32]. Its air pollution potential has been assessed [182]. Atmospheric oxidation of alkyl halides is reported to have a half-life of less than 20 hours, while the half-life of HO radical attack is 234 days [8]. Ethylene dibromide has a boiling point of 131.6°C and a vapor pressure of 11 mm at 25°C [181].

---

[181] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 1977. pp. 195-209.

[182] Johns, R. Air Pollution Assessment of Ethylene Dibromide. National Technical Information Service No. PB 256 736, 1976.

Ethylene Dichloride

Ethylene dichloride (1,2-dichloroethane, ethylene chloride; CAS No. 107-06-2) has been found in preliminary results to be carcinogenic when fed to male and female rats by the National Cancer Institute [183]. Rats fed ethylene dichloride had a significant excess of site-specific malignant and nonmalignant tumors. In other studies it has been negative by inhalation in rats, guinea pigs and monkeys but mutagenic to fruit flies [184]. Because of the positive animal studies, it is included on the probable carcinogen list for this project.

Production and Persistence

It is estimated that 6.7×10^7 kg ethylene dichloride is emitted per year from stationary sources [1]. Other references cite a production of 3.9×10^9 kg produced with 2.1×10^8 kg released [7], 4.2×10^9 kg (1973) [6] produced, and production of 4.2×10^9 kg, 3.6×10^9 kg, and 3.6×10^9 kg in 1974, 1975, and 1976 [32]. An air pollution assessment of ethylene dichloride has been made [184]. Ethylene dichloride reacts slowly with peroxides with a half-life of 1,000 days and is resistant to photochemical degradation [184]. The HO reaction half-life has been estimated to be 234 hours [8]. It has a boiling point of 83.5°C and a vapor pressure of 61 mm at 20°C [33].

---

[183] New Findings on Two Carcinogens Reported to Subcommittee by NIOSH. Occupational Safety & Health Reporter, 7(35):1331, 1978.

[184] Johns, R. Air Pollution Assessment of Ethylene Dichloride. National Technical Information Service No. PB 256 733, 1976.

Ethylene Glycol

Although ethylene glycol (1,2-ethanediol) has been reported to give neoplastic effects at 4 g/kg on mouse skin [6], no other confirming reports of carcinogenicity or mutagenicity have been found. Many reports indicate that ethylene glycol is noncarcinogenic in different species by various routes of administration. These include 18 tests reported in 8 articles before 1950 on rats, mice, and rabbits in food, drinking water, intravenously, subcutaneously, intermuscularly, and via inhalation - all with negative results [26].

More recently, tests have been negative for ethylene glycol [185] including subcutaneous rat tests [186], subcutaneous newborn mice tests [187], and inhalation tests using rat, guinea pig, rabbit, dog, and monkey [188]. It is also negative in the *Salmonella* test for mutagens [32, 52]. All in all, ethylene glycol will be considered a noncarcinogen for this project.

---

[185] Homburger, F. Carcinogenicity of Several Compounds. National Technical Information Service No. PB 183 027, 1968. 26 pp.

[186] Mason, M. M. Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines. National Technical Information Service No. PB 195 185, 1969. 55 pp.

[187] Derse, P. H. Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety. National Technical Information Service No. PB 195 153, 1969. 135 pp.

[188] Coon, R., et al. Animal Inhalation Studies on Ammonia, Ethylene Glycol, Formaldehyde, Dimethylamine, and Ethanol. Toxicol. Appl. Pharmacol., 16(3):645-646, 1970.

Ethylene Oxide

Ethylene oxide (oxirane, 1,2-epoxyethane; CAS No. 75-21-8) has been found negative on skin-painted mice and subcutaneously injected rats [189]. Short-term inhalation tests (6 months) on dogs, mice, rats, rabbits, guinea pigs, and monkeys were negative [189]. An excess of tumors was found in mice exposed to ethylene oxide-treated ground-corncob bedding as an experiment not designed to test for carcinogenicity of ethylene oxide [189]. Ethylene oxide is a mutagen in *S. typhimurium*, *Neurospora crassa* and *Drosophila melanogaster* tests [32, 189]. It will be considered a possible carcinogen for this project based on the *in vitro* mutagenicity data.

Production and Persistence

It is estimated that 4.5×10^6 kg ethylene oxide is emitted per year from stationary sources [1]. Other estimates of production include 1.8×10^9 kg produced with 4.5×10^7 kg released [44], 1.8×10^9 kg produced [6], 1.8×10^9 kg produced in 1974 [8], 1.9×10^9 kg produced in 1975 [189], and 1.8×10^9 kg and 2.0×10^9 kg produced in 1974 and 1975 [32]. Its primary use as an intermediate is expected to grow at 4.7-5.2% per year until 1980 [32]. Dispersed in the atmosphere, epoxides would be oxidized by HO radicals with a 3- to 11-hour half-life [8]. Its reaction with HO radicals has also been estimated to give half-lives of 1.6 days [44] and 23 hours [8]. It has a boiling point of 11°C and a vapor pressure of 1,095 mm at 20°C [33].

---

[189] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 157-167.

Ethylenimine

Ethylenimine (Aziridine, CAS No. 151-56-4) is well documented as being a potent mutagen, and it is used as a mutagen in many plant studies (533 references on TOXLINE to its use as a mutagen or carcinogen). It has also been found to be carcinogenic in at least two strains of mice following oral administration, producing liver-cell and pulmonary tumors [190]. Subcutaneous injection of single doses in suckling mice produced increased incidence of lung tumors in males. Subcutaneous injection in oil produced local tumors in rats [190]. It is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 2.7 x 10^4 kg is released to the environment per year [44]. Estimates of production are 2.3 x 10^6 kg, 1.4 x 10^6 kg, 2.2 x 10^6 kg (1974), and 2.3 x 10^6 kg per year [6, 8, 32, 44]. Ethylenimine is infinitely soluble in water [6], basic, and polar, and could therefore be expected to be very slow to escape from water to the atmosphere [8]. Its reaction with HO in the atmosphere has been found to have a half-life of 1.5 days [44], 47 hours [8], and 56 hours [8]. It has a boiling point of 56°C and a vapor pressure of 160 mm at 20°C [190].

---

[190] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 9, 1976. pp. 37-46.

Fluoranthene

Fluoranthene (CAS No. 206-44-0) was tested for carcinogenicity in 1935 and 1938 on mice by skin (0.3% in benzene for 501 days) and oral (10 mg for 18 months) routes of administration with negative results [5]. Arcos and Argus reported in 1974 that in 1963 or 1964 others had found fluoranthene negative by subcutaneous tests in XVII nc/Z strain of mice [191]; fluoranthene is generally considered noncarcinogenic [191]. Recent tests of mouse skin application, alone or followed by croton oil, were negative after 15 months and 20 weeks, respectively [192]. It has been tested on TA98, 100 and 1537 strains of *S. typhimurium* for mutagenicity [193]. It is considered a probable noncarcinogen for this project.

[191 Arcos, J. C., and M. F. Argus. Chemical Induction of Cancer, Volume 11A. Academic Press, New York, 1974. pp. 26, 237.

[192] Hoffman, D., et al. J. Natl. Cancer Inst., 49:1165-1175, 1972.

[193] Rao, T. K., et al. Environmental Mutagenesis of Energy-Related Effluents. Genetics, 83:S60, 1976.

Formaldehyde

Formaldehyde (methanal, formalin, methyl aldehyde; CAS No. 50-00-0) has been tested for carcinogenicity with negative results on many animal species in short-term (usually less than a year) tests [5]. However, 1,300 mg/kg (65 weeks) caused neoplastic effects in rats [6], and 1 ml of 0.4% formaldehyde solution caused spindle cell sarcomas and fibrosarcomas at the injection site of 4/10 rats evaluated at least 649 days [194]. Formaldehyde has been shown to be a mutagen in *Drosophila melanogaster*, *E. coli*, barley, *Vicia faba*, yeast, and viral transformation enhancement tests [4, 44, and personal communication with B. C. Casto on 9 February 1978], but negative on the mouse dominant lethal test [30]. For this project formaldehyde will be considered a possible carcinogen.

Production and Persistence

It is estimated that 4.1 x 10^7 kg formaldehyde is emitted per year from stationary sources with 82% of this being from charcoal manufacture and catalytic cracking in petroleum refining [1]. Other estimates of production include 2.6 x 10^9 kg produced and 2.4 x 10^7 kg released [6], 2.6 x 10^9 kg produced and 6.4 x 10^7 kg released [44], 2.6 x 10^9 kg produced (1974) [8], and 2.9 x 10^9 kg and 2.6 x 10^9 kg produced in 1973 and 1975 [32]. The production of formaldehyde is projected to grow by 4-5% per year in the next 5 years [32]. In solution it is essentially nonvolatile, but in air it will react with HO radical with a half-life of 2.6 hours [8] or 1.2 hours [44]. As a gas it has a boiling point of -21°C and a vapor pressure of 1,946 mm at 25°C [6]. Its environmental fate and biological and environmental effects have been studied [195].

---

[194] Watanabe, F., et al. Gann, 45:451-452, 1954 (as cited in Reference 5).

[195] Investigation of Selected Potential Environmental Contaminants: Formaldehyde. National Technical Information Service No. PB 256 839, 1976.

Guthion

Guthion has been found to be mutagenic in that it induced chromosome breaks in diploid [WI-38 (female embryonic lung)] and heteroploid [HE_p-2 (male neoplastic larynx)] cells [196]. Guthion also increased mitotic recombination in *S. cerevisiae* [169]. However, it did not prove to be a mutagen in *S. typhimurium* assays [169] or in *E. coli* or *B. subtilis* systems [169] and did not induce dominant lethal effects in mice [197]. For this project it is considered a noncarcinogen.

---

[196] Alam, M. T., and S. S. Kasatiya. Cytological Effects of an Organic Phosphate Pesticide on Human Cells *in Vitro*. Can. J. Genet. Cytol., 18(4):665-671, 1976.

[197] Jorgenson, T. A., et al. *In Vivo* Mutagenesis Investigations of Ten Commercial Pesticides. Toxicol. Appl. Pharmacol., 37(1):109, 1976.

Heptachlor

The IARC monograph on heptachlor (heptachloro-tetrahydro-methanoindene, CAS No. 76-44-8) shows this compound to have both positive and negative data, with more negative than positive [198]. It is a mutagen as tested by the enhancement of viral transformation (personal communication with B. C. Casto on 9 February 1978). Recent NCI tests [199] with rats and mice demonstrated that heptachlor is a carcinogen for the liver in mice under the conditions of their bioassay. It is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1.1 x 10^4 kg heptachlor is emitted per year from stationary sources [1]. Estimates of production include 2.7 x 10^6 kg (1971) and 2.7 x 10^6 kg produced [6]. It has a melting point of 95°C and a vapor pressure of 3 x 10^{-4} mm at 25°C [198].

---

[198] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 173-191.

[199] Bioassay of Heptachlor for Possible Carcinogenicity, CAS No. 76-55-8. National Technical Information Service No. PB 271 967.

Hexachlorobenzene

Hexachlorobenzene (benzene hexachloride, CAS No. 118-74-1) induces microsomal enzymes [129], is only slightly teratogenic [200], and tests positive/negative [30] and negative [200] on the dominant lethal test in rats. When fed to rats it was noncarcinogenic [201], and by *S. typhimurium* tests (using mouse liver microsomes) it was negative [172].

Hexachlorobenzene was, however, mutagenic when tested with *S. cerevisiae* at 100 ppm [202], and when fed to 6-week-old Syrian golden hamsters at concentrations up to 200 ppm it induced hepatomas, hemangiomas and thyroid adenomas in a dose response manner [203]. It is therefore considered a possible carcinogen for this project.

Production and Persistence

It has $t_{1/2}$ $\sim$2 days in the air, reacting with OH to form pentachlorophenol. Its production is estimated to be 6×10^5 kg per year, and 1.3×10^5 kg is used in a dispersive manner as a fungicide for a total of 2.2×10^5 kg released [7]. It has a boiling point of 332-326°C [33].

---

[200] Khera, K. S. Hexachlorobenzene: Teratogenicity and Dominant Lethal Studies in Rats. Toxicol. Appl. Pharmacol., 29(1):109, 1974.

[201] Boyland, E., et al. Kidney Tumors in Rats Following Treatment with 2-Acetylaminofluorene, Tryptophan, and 14-Saccharolactone and the Failure of Substances Which Cause Porphyrinuria to Induce Tumors. In: British Empire Cancer Campaign 1963 - Part 2: Scientific Report, 1963. pp. 58-59.

[202] Guerzoni, M. E., et al. Mutagenic Activity of Pesticides. Riv. Sci. Tecnol. Alimenti Nutr. Um. (Ital.), 6(3):161-165, 1976.

[203] Cabral, J. R. P., et al. Carcinogenic Activity of Hexachlorobenzene in Hamsters. Nature, 269(5628):510-511, 1977.

Hexachlorobutadiene

Hexachlorobutadiene injected I.P. in mice apparently caused no lung adenomas [204]. A study with rats on diets containing hexachlorobutadiene showed no effects at 0.2 mg/kg/day or less, but renal tubular adenomas and adenocarcinomas at 2 and 20 mg/kg/day [205, 206]. A reproduction study also showed no effects at 0.2 but effects at 20 mg/kg/day. At the high doses some toxicity was also evident. A 90-day feeding study (0.3-30 ppm) on Japanese quail showed little effect of this chemical [207]. NIOSH has a safety alert out on the basis of the above tests, and hexachlorobutadiene is considered a possible carcinogen for this study.

production and Persistence

It is estimated that 3.6×10^6 kg is produced in the United States with 3.3×10^6 kg being released per year [7]. It reacts with OH and O_3 with a $t_{1/2}$ of less than 1 day and has a low water solubility [7]. The boiling point of hexachlorobutadiene is 210°C with a vapor pressure of 22 mm at 100°C [33].

---

[204] Test for Carcinogenicity of Organic Contaminants of United States Drinking Waters by Pulmonary Tumor Response in a Strain of Mice. Cancer Res., 37(8):2717-2720, 1977.

[205] Results of a Two-year Chronic Toxicity Study with Hexachlorobutadiene in Rats (Meeting Abstract). Toxicol. Appl. Pharmacol., 41(1):204, 1977.

[206] Kociba, R. J., et al. Results of a Two-Year Chronic Toxicity Study with Hexachlorobutadiene in Rats. Am. Ind. Hyd. Assoc. J., 38(11):589-602, 1977.

[207] Reproduction Study in Japanese Quail Fed Hexachlorobutadiene for 90 days. Toxicol. Appl. Pharmacol., 30(2):255-265, 1974.

Hexamethylenetetramine

Hexamethylenetetramine (CAS No. 100-97-0) has been extensively tested in both rats and mice [5]. Almost all of these tests show that this chemical is noncarcinogenic when given either orally (up to 5% of drinking water) or subcutaneously (25 g/kg) [208]. It has been tested on *E. coli* differential growth (pol A) test with positive results which was considered a false positive [46]. It has also been reported to be nonmutagenic to *Drosophila*, positive in oral mouse dominant lethal test, negative in an intraperitoneal mouse dominant lethal test, and positive on a chromosomal abberation test in cultured lymphocytes [32]. Hexamethylenetetramine will be considered a noncarcinogen (with some positive data) for this project because of the extensive negative animal data.

---

[208] Della Porta, G., et al. Non-Carcinogenicity of Hexamethylenetetramine in Mice and Rats. Food Cosmet. Toxicol., 6(6):707-715, 1968.

Hydrazine

Hydrazine (diamine, CAS No. 302-01-2) has been shown to be carcinogenic in mice after oral and intraperitoneal administration and in rats following oral administration [209]. It was negative in hamsters after oral administration [209]. Hydrazine is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 3.5 x 10^3 kg hydrazine is emitted per year [1]. In 1966, production of hydrzine was 7 x 10^6 kg per year with more than 70% of this going toward rocket fuels [209]. Production was estimated at 1.4 x 10^6 kg in 1971 and at 1.7 x 10^7 kg in 1974 [8, 32]. The demand for hydrazine is expected to increase 15-17% a year until 1985 [32]. Hydrzine is polar, nonvolatile and water soluble, suggesting that it will not transfer to the atmosphere at significant rates [8]. Oxidation by HO radicals in the gas phase is reported to be rapid with a half-life of less than 1 hour [8]. It has a boiling point of 113°C and a vapor pressure of 16 mm at 20°C [33].

---

[209] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 5, 1974. pp. 127-136.

Hydroquinone

Hydroquinone is listed on the NIOSH Suspected Carcinogen List, but it is apparently there by mistake. The 1955 reference cited [210] shows 20 mg of hydroquinone applied to the skin of mice (in benzene) developed only 1 tumor out of 22 surviving mice as compared with 1 tumor out of 22 surviving mice for the croton oil control. A more recent reference cites hydroquinone as a bladder carcinogen when implanted in cholesterol pellets, producing 32% tumors vs 12% for the cholesterol control [211]. Hydroquinone is said to be an inhibitor of 3,4-benzopyrene carcinogenesis [212], inactive as a promoter [213], and slightly active as a promoter [214] of carcinogenesis.

Hydroquinone has been reported as more toxic to repair deficient *E. coli* (pol A^-) indicating that it may induce DNA damage [32], but negative in inducing antibiotic resistance in *Micrococcus* pyrogens [32]. Chromosome aberrations have been noted in several plant systems after treatment with hydroquinone [32]. These mutagenic references almost place hydroquinone on the possible carcinogen list, but they involve test systems which have not been extensively evaluated. Hydroquinone will be considered a probable noncarcinogen (with some significant positive data) for this project.

---

[210] Roe, F. J. C., and M. H. Salaman. Further Studies on Incomplete Carcinogenesis. British J. of Cancer, 9:177-203, 1955.

[211] Boyland, E., et al. Further Experiments on Implantation of Materials into the Urinary Bladder of Mice. British J. of Cancer, 18:575-581, 1964.

[212] Van Duuren, B. L., and B. M. Goldschmidt. Cocarcinogenic and Tumor-Promoting Agents in Tobacco. J. Natl. Cancer Inst., 56:1237-1242, 1976.

[213] Hecht, S. S., et al. Study of Tobacco Carcinogenesis; XIII: Tumor-Promoting Subfractions of the Weakly Acidic Fraction. J. Natl. Cancer Inst., 55(6):1329-1336, 1975.

[214] Interaction Between Hydroquinone and Cigarette Smoke Condensate in Short-Term Skin Tests for Carcinogenicity. TOXLINE.

Kelthane

Kelthane has been found nonmutagenic to *E. coli* bacteria in the WP2 TYR to prototrophy test [139]. It is considered a probable noncarcinogen for this project.

Malathion

Malathion has been demonstrated not to be a teratogen [134], and Ames et al. consider it not to be a mutagen [52]. It has been found to be nonmutagenic in four test systems [18], and a study by the National Cancer Institute found it to be noncarcinogenic to rats and noncarcinogenic to mice [215]. Malathion was found nonmutagenic by a dominant lethal test in mice [197] but was a slight promoter in rats when given with dimethylbenz(a)anthracene [216]. For this project Malathion is classed as a probable noncarcinogen.

---

[215] National Cancer Institute Draft Summaries of Bioassay Reports. Chem. Reg. Rep., 1(45):1602-1603, 1978.

[216] Silinskas, K. C., and A. B. Okey. Protection by DDT Against Mammary Tumors and Leukemia During Prolonged Feeding of 7,12-Dimethylbenz(a)anthracene to Female Rats. J. Natl. Cancer Inst., 55(3):653-658, 1975.

Maleic Anhydride

Only one 1963 reference cites maleic anhydride as a carcinogen [217]. In this paper three rats of an unspecified species were injected 550 times with maleic anhydride. Two of the three rats developed fibrosarcomas at the injection site. No other indications could be found in the literature suggesting that maleic anhydride may be a mutagen or a carcinogen in any test systems. In the atmosphere maleic anhydride could be expected to be converted rather rapidly to maleic acid for which no evidence has been found to suggest it has any carcinogenic or mutagenic potential. Since maleic anhydride has some degree of toxicity and is a lacrimator, animal studies will probably show it to be a noncarcinogen.

---

[217] Dickens, F., and H. E. H. Jones. Further Studies on the Carcinogenic and Growth-Inhibitory Activity of Lactones and Related Substances. Brit. J. Cancer, 17:100-108, 1963.

Mercaptobenzothiazole

Mercaptobenzothiazole (2-benzothiazolethiol, Captax; CAS No. 149-30-4) was one of the 80 chemicals evaluated as having the greatest potential for environmental effects [7]. This report cited a negative mice feeding study [77] in which two groups of 36 mice of slightly different strains were given 464 mg/kg mercaptobenzothiazole in gelatin orally on days 7-28 and then 1,492 ppm in their diet for 17 months with no increase in tumors found. Seventeen months is a little on the short side for carcinogen evaluation by present standards.

In another study [69] mercaptobenzothiazole was given orally and subcutaneously at 100 and 215 mg/kg, respectively, to two mouse strains (36 mice per strain). It was found to cause a statistically significant (0.01 level) increase in type A reticulum cell sarcomas when given subcutaneously. It may have been tested for mutagenicity [218] and teratogenic activity, but the results are unclear [219]. Because of the limited tests thus far conducted, more *in vivo* or *in vitro* data might change its classification but it will be considered a possible carcinogen for this project.[a]

Production and Persistence

The production of mercaptobenzothiazole is estimated at 2.7×10^6 kg per year with the release of 2.7×10^4 kg per year [7]. It is reactive towards RO ($t_{1/2}$ = 8 days), HO ($t_{1/2}$ = 1 day), and O_3 ($t_{1/2}$ = 9.6 hr) [7].

---

[a] The *S. typhimurium* mutagenicity test has recently been conducted on mercaptobenzothiazole with negative results (personal communication with Paul Graham, Monsanto Company, on 26 January 1979). This information would most likely have changed the classification given to mercaptobenzothiazole to probable noncarcinogen by the criteria used in this report.

- - - - - - - - - - -

[218] Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume III. National Technical Information Service No. PB 223 161, 1968.

[219] Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume II. National Technical Information Service No. PB 223 160, 1968.

Methyl Bromide

Methyl bromide has been tested on barley and is said to be a methylating compound [220]. No other references were found on the mutagenic or carcinogenic potential of methyl bromide, so it has been placed on the probable noncarcinogen list.

---

[220] Ehrenberg, L., et al. On the Reaction Kinetics and Mutagenic Activity of Methylating and Beta-Halogenoethylating Gasoline Additives. Radiat. Bot., 14(3):185-194, 1974.

Methyl Chloride

No data have been found indicating that methyl chloride (chloromethane, CAS No. 74-87-3) is a carcinogen (e.g., TOXLINE, CANCERLINE, and Reference 5). However, it does appear to be a mutagen to *S. typhimurium* [14]. Because of the close correlation between mutagens and carcinogens, methyl chloride has been placed on the possible carcinogen list.

Production and Persistence

It is estimated that 2.3 x 10^7 kg methyl chloride is emitted per year from stationary sources [1]. Another estimate [44] is 7.6 x 10^6 kg/year released from a production of 2.1 x 10^8 kg. Other production estimates are 2.1 x 10^6 kg, and 2.2 x 10^6 kg, 1.6 x 10^6 kg and 1.7 x 10^6 kg produced in 1974, 1975, and 1976, with a projected growth of 6% per year [6, 32]. Reaction in the atmosphere with the HO radical is slow, with a half-life of about 1 year [44]. It takes 27 minutes for 50% of a 1-ppm water solution to evaporate at 25°C [33]. Methyl chloride has a boiling point of -24°C and a vapor pressure of 3,800 mm (5 atm) at 20°C and 2,150 mm (2.83 atm) at 25°C [6, 33].

Methyl Ethyl Ketone

Methyl ethyl ketone (MEK, 2-butanone) is included on the NIOSH Suspected Carcinogen List because of a teratogenic reference and as a priority pollutant. MEK does appear to be embryotoxic, fetotoxic, and perhaps teratogenic when tested at high concentrations (1,000-3,000 ppm) [150, 221]. Rat feeding studies conducted in 1939 and 1940 were negative [222, 223]. Mouse skin application tests in 1965 of mixtures containing MEK were generally negative in the absence of benzo(a)pyrene [224]. MEK has also been tested on TA 1535, 1536, 1537, and 1538 strains of *S. typhimurium* bacteria (Ames Test) and on *E. coli* WP2-try mutagen tests with both being negative [157]. No other references could be found on TOXLINE or CANCERLINE indicating that MEK is a mutagen or a carcinogen. It is considered a probable noncarcinogen for this project.

---

[221] Embryo Toxicity and Feto Toxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane, and Methyl Ethyl Ketone in Rats. Toxicol. Appl. Pharmacol., 29(1):123, 1974.

[222] Nakahara, W., and K. Mori. Proc. Imp. Acad., Japan, 15:278-281, 1939 (as cited in Reference 5).

[223] Nakahara, W., and K. Mori. Gann, 34:143-145, 1940 (as cited in Reference 5).

[224] Horton, A. W., et al. Cancer Research, 25:1759-1763, 1965 (as cited in Reference 5).

Methyl Methacrylate

Methyl methacrylate is on the NIOSH Suspected Carcinogen List because of a paper which shows that 0.25 mg/kg of the compound (1/5 LD_{50}) caused 8% of the rat fetuses to have gross abnormalities (hemangiomas) but no skeletal malformation [225]. A search of the literature could find no other references indicating methyl methacrylate to be a mutagen or a carcinogen. It is therefore listed as a probable noncarcinogen for this project.

---

[225] Singh, A. R., et al. Embryonic-Fetal Toxicity and Teratogenic Effects of a Group of Methacrylate Esters in Rats. J. Dental Research, 51:1632-1638, 1972.

4,4'-Methylene Bis(2-chloroaniline)

4,4'-Methylene bis(2-chloroaniline) or MOCA (CAS No. 101-14-4) has been found to be a carcinogen in mice and rats after oral administration and produces distant tumors in the rat after subcutaneous administration [226]. It is an OSHA regulated carcinogen [227]. Many other positive references are found in TOXLINE and CANCERLINE and it is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 4.5×10^4 kg is emitted per year from a 3×10^6 kg production [56]. Other estimates of production are $1.5\text{-}2.5 \times 10^6$ kg in 1970 [226] and 3.5×10^6 kg in 1972 [6, 8, 226]. The reaction with the HO radical in the atmosphere is estimated to yield a half-life of 12 hours [8] or 1 day [56], while the O_3 half-life is 1 day [56] and the RO_2 half-life is 39 days [56]. It is said to have a melting point of 110°C [226] and a negligible vapor pressure [6].

---

[226] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 65-71.

[227] OSHA Compliance Guide, 29 CFR Part 1910, 1978.

Methylene Chloride

There are no positive data on methylene chloride (dichloromethane) in TOXLINE or CANCERLINE. Interim results of carcinogenic tests in a 2-year inhalation study involving nearly 2,000 animals exposed to concentrations of methylene chloride as high as 3,500 ppm were negative [228]. One recent paper cites methylene chloride as being positive in the Ames test [229]. Methylene chloride is still considered a noncarcinogen for this project until further testing is completed because of the negative NCI animal data.

---

[228] Methylene Chloride Passes Early Tests. Chem. Eng. News, 55(19):6, 1977.

[229] Mutation Research, Volume 53, January 1978.

Methylenedianiline

The IARC monograph [230] on methylenedianiline [4,4-diaminodiphenyl methane, bis (*p*-aminophenyl)methane; CAS No. 101-77-9] indicates both positive and negative data have been obtained from animal testing of the compound. Given orally to rats, it was found to be noncarcinogenic. Methylenedianiline is on the NIOSH safety alert list because of some significant positive results [231, 232] and it can at least be considered a possible carcinogen for this project.

Production and Persistence

It is estimated that 2.6 x 10^4 kg is emitted per year from stationary sources [1]. The production has been estimated to be 5 x 10^5 kg, 7 x 10^5 kg, and 1 x 10^6 kg in 1965, 1966, and 1972 [230]. It has a melting point of 93°C and a boiling point of 231°C at 11 mm [33].

---

[230] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 79-85.

[231] Schoental, R. Carcinogenic and Chronic Effects of 4,4'-Diaminodiphenylmethane, an Epoxyresin Hardener. Nature, 219:1162-1163, 1968.

[232] Steinhoff, D., and E. Grundmann. Zur Cancerogenen Wirkung von 4,4'-Diaminodiphenylmethan und 2,4'-Diaminodiphenylmethan. Naturwissenschaften, 57:247-248, 1970.

Methylstyrene

One reference cited in the NIOSH Suspected Carcinogen List shows methylstyrene to be a teratogen [233]. Permissible exposure limits have been determined for methylstyrene [234]. Application of methylstyrene to rabbit [235] inhalation or rat skin [235, 236] demonstrated only a reversible [236] irritating response to the chemical. Other toxic responses have been noted in rats, rabbits [237], and housefly larvae [238], but no indication of carcinogen or mutagenic responses were found on TOXLINE or CANCERLINE.

---

[233] Gigiena i Sanitariya, 34:40, 1969. (Translated in Hygiene and Sanitation.)

[234] Toxic Substances: Proposed Occupational Safety and Health Standards for Alkyl Benzenes, Cyclohexane, Ketones, and Ozone. Fed. Regist. 40(196):47262-47313, 1975.

[235] Effect of Alpha-Methylstyrene and Tert-Dodecyl Mercaptan on the Skin of Animals. Vop. Gig. Tr. Profzabol., Mater. Nauch. Konf.; 1972. pp. 247-249.

[236] Reversible Damage to the Skin of Experimental Animals Subjected to the Inhalation of Butadiene and Alpha-Methylstyrene. Mater. Nauch. Sess., Posoyashck. 50-Letiyu Obrazov. SSSR, Omsk. Gas. Med. Inst.; 1972. pp. 871-873.

[237] Effect of Isopropylbenzene and Alpha-Methylstyrene on Leucopoiesis. Farmakol. Toksikol., 35(4):491-492, 1972.

[238] Effect of the Wastes from Phenol Production on Housefly Larvas. Mater. Konf. Molodykh. Uch. Stud., Posvyashch. 50-Letiyu SSSR; 1973. pp. 375-377.

Morpholine

Morpholine (diethyleneimide oxide, tetrahydro-1,4-isoxazine; CAS No. 110-91-8) is cited in one reference as causing neoplastic effects in the mouse after oral administration of 6.33 g/kg over 28 weeks [6]. This refers to a study (with no control animals) in which 40 Swiss mice (20M, 20F) were given neutralized morpholine in their food [239]. After 40 weeks, 5 malignant lymphomas and 5 lung adenomas were found in the surviving 38 animals. (When given in combination with sodium nitrite, many more tumors were found.)

In another study, 100 g/kg morpholine as 0.5% of the diet for rats produced no tumors, but 0.5% sodium nitrite added gave 7 tumors [240]. Many other studies have been conducted with sodium nitrite added to produce nitrosomorpholine *in vivo* and *in vitro*. In Russian studies, morpholine in the air in 0.008-0.07 mg/l concentrations for 4 months caused mutagenic chromosomal aberrations in bone marrow cells in rats [241] and guinea pigs [242]. The future classification of morpholine requires more data, but for this project it will be considered a possible carcinogen.

Production and Persistence

It is estimated that 1 x 10^7 kg is produced and 5.5 x 10^6 kg is emitted per year [6].

---

[239] Greenblatt, M., et al. J. Natl. Cancer Inst., 46(5):1029-1034, 1971 (as cited in Reference 5).

[240] Sander, J., and G. Bunkle. Z. Krebsforsch, 73(1):54-66, 1969.

[241] Fomenko, V. N., and E. E. Strekalova. Mutagenic Action of Some Industrial Poisons as a Function of Concentration and Exposure Time. Toksikol. Nov. Prom. Khim. Veshehestv., 13:51-57, 1973 (CA 79:143228).

[242] Migukina, N. V. Evaluation of the Danger of Morpholine During Chronic Action. Toksikol. Nov. Prom. Khim. Veshehestv., 13:92-100, 1973 (CA 79:143345).

Naphtha

Naphtha (coal tar naphtha) is cited in Reference 6 as a recognized carcinogen. Actually, naphthas vary in composition depending on their source, with coal tar naphtha being mainly benzene and its homologs. From other sources naphtha could be principally paraffins, methanol and acetone, or gasoline. Even as a mixture naphtha is not found in Reference 5. Of the primary ingredients of naphtha, only benzene is a recognized carcinogen, and since benzene is covered separately, naphtha will be dropped from consideration.

1-Naphthylamine

1-Naphthylamine (alpha-naphthylamine, CAS No. 134-32-7) no carcinogenic effect when given orally to hamsters, and both oral and subcutaneous tests with mice gave inconclusive results [243]. In dogs, it was demonstrated that 1-naphthylamine, if carcinogenic at all, was less so than the 2-isomer [243]. Other tests on dogs [26], hamsters, mice, rats, and rabbits [112] show that 1-naphthylamine may be carcinogenic and that it is generally contaminated with the 2-isomer, which is a potent carcinogen [243, 244]. It is an OSHA regulated carcinogen (Code of Federal Regulations 29 CFR 1910.1004) whether or not it is truly a carcinogen [244]. It is also positive on the *S. typhimurium* test [52] and on an enhancement of viral transformation test (personal communication with B. C. Casto on 9 February 1978). For these reasons, it is considered a possible carcinogen for this project.

Production and Persistence

Production has been estimated to be 5×10^5 kg in 1963 [6] and 3.2×10^6 kg in 1974 [8]. It reacts with oxidizing materials in the atmosphere [6] and reacts with the HO radical in air with a 12-hour half-life [8]. It has a boiling point of 300.8°C and a vapor pressure of 1 mm at 104.3°C [6].

---

[243] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 1974. pp. 87-96.

[244] OSHA Compliance Guide, 29 CFR Part 1910, 1004, 1978. pp. 298-300.

Naphthalene

Naphthalene (CAS No. 91-20-3) has generally been negative when given to rats and mice by various routes of administration (including 10 g total oral dose over 33 months) with only a few tumors reported by other authors in experiments without control animals [5]. It is generally considered to be a noncarcinogen by various authors [245]. It has been tested in G46 *S. typhimurium* and K-12 *E. coli* strains [246]. Another reference reports negative results for *S. typhimurium* strains TA 98, 100, 1535 and 1537 [52]. Naphthalene is considered a probable noncarcinogen for this project.

---

[245] Arcos, J. C., and M. F. Argus. Chemical Induction of Cancer, Volume IIA. Academic Press, New York, 1974. pp. 194, 237, and 278.

[246] Kraemer, M., et al. *S. Typhimurium* and *E. Coli* to Detect Chemical Mutagens. Naunyn-Schmiedebergs Arch. Pharmakol., 284:46R, 1974.

Naphthoquinone

Naphthoquinone is on the NIOSH Suspected Carcinogen List because of a 1940 Japanese reference [62]. In this paper α-naphthoquinone (in benzene) painted daily on the backs of mice caused 3/77 skin cancers and 11/77 papillomas compared to 0/46 skin cancers and 1/46 papillomas for benzene alone on mice surviving 200 days. β-Naphthoquinone produced no cancers or papillomas out of 25 mice surviving 200 days.

A survey of recent literature from TOXLINE, CANCERLINE, and Reference 5 found no pertinent references. Since the only positive reference is outdated and reports the use of benzene as the solvent, naphthoquinone is being placed on the probable noncarcinogen list for this project.

1-Naphthyl Methylcarbamate

The primary reference to this compound's carcinogenic potential from a Russian journal has not been obtained. Another Russian reference from the same year [247] declares that 2-naphthyl methylcarbamate is carcinogenic while 1-naphthyl methylcarbamate is noncarcinogenic. 1-Naphthyl methylcarbamate tested on male and female mice of two strains was found to be noncarcinogenic [69]. No other references were found in CANCERLINE to indicate that this chemical is a carcinogen. There are negative mice feeding studies (18 months) and rat intergastric studies reported [5]. It is probably a noncarcinogen based on the available literature.

---

[247] Zabezhinskiy, M. A. Investigations on Possible Carcinogenic Effects of Beta-Sevin. Vopr. Onkol., 16(11):106-107, 1970.

Nitrobenzene

Although on structural basis nitrobenzene (CAS No. 98-95-3) has been predicted to be a carcinogen, there was no positive indication from actual tests of the chemical cited in "Air Pollution Assessment of Nitrobenzene" [248] or on CANCERLINE or TOXLINE. It has been reported to induce sex-linked recessive lethal mutations in *Drosophila melanogaster* when administered as a vapor for 8-10 days [32]. With only one *in vitro* positive test reported, nitrobenzene will be considered a noncarcinogen (with some positive data) for this project.

---

[248] Dorigan, J., and J. Hushon. Air Pollution Assessment of Nitrobenzene. National Technical Information Service No. PB 257 776, May 1976.

Nitrophenol

No data on the carcinogenicity of nitrophenols could be found on CANCERLINE or TOXLINE, but *p*-nitrophenol has been found to be mutagenic by one test system and nonmutagenic by five other test systems [18]. When comparing *S. typhimurium* test results with other systems, Ames classified nitrophenol as a nonmutagen [52]. For this project, nitrophenols will be classed as probable noncarcinogens.

Nitrosodimethylamine

There are many data showing nitrosodimethylamine (dimethylnitrosoamine) to be a potent carcinogen [249]. It has, therefore, been placed on the probable carcinogen list for this project. In the final selection of carcinogens, however, it may not be advantageous to select this compound. This is because nitrosodimethylamine rapidly decomposes in sunlight [250], under normal conditions is of no significance as an air pollutant [250], and has generally been found only in the air near certain manufacturing plants which had (now repaired) leaks in their systems [251].

Production and Persistence

Nitrosodimethylamine is emitted in less than 100-kg year quantities from the dimethylhydrazine stationary sources [1]. One estimated of production is less than 450 kg/year [8]. Photolysis of nitrosodimethylamine is reported to be rapid with a half-life of less than 1 hour [8]. It has a boiling point of 152°C [33].

---

[249] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 1, 1972. pp. 95-106.

[250] Bretschneider, K., and J. Matz. Occurrence and Analysis of Nitrosamines in Air. IARC Sci. Pub. No. 14, 1976. pp. 395-399.

[251] Fine, D. H., et al. N-Nitroso Compounds in Air and Water. IARC Sci. Pub. No. 14, 1976. pp. 401-408.

Nitrochlorobenzene

Nitrochlorobenzene (chloronitrobenzene) has been found to mutate *S. typhimurium* [252] and is indicated as a carcinogen causing neoplasms in another reference's summary sheets while listed as not tested in an appendix to the same reference [6]. For this project it will be considered a possible carcinogen.

Production and Persistence

It is estimated that 3×10^2 kg nitrochlorobenzene is emitted per year from stationary sources [1]. An estimate of production is 6.4×10^7 kg of each of the isomers produced in 1967 [6]. Nitrochlorobenzene reacts with oxidizing materials in the atmosphere [6]. In the soil, microflora decomposes this chemical in 64 days [1]. The *m*-, *p*-, and *o*-isomers have boiling points of 236, 242, and 245°C with a vapor pressure of 10 mm at 25°C [33].

---

[252] Tardiff, R. G., et al. Halogenated Organics in Tap Water: A Toxicological Evaluation. In: The Environmental Impact of Water Chlorination, National Technical Information Service No. CONF 751096, 1976. pp. 213-228.

Parathion

Nothing was found in CANCERLINE to indicate that parathion is a mutagen or carcinogen. The NIOSH Suspected Carcinogen List reference cites parathion as being a slight teratogen only when given in sufficient quantitiy as to cause toxic poisioning to be apparent in the dams [134]. It has been found to be nonmutagenic by several different *in vitro* tests [18], but does cause an antimitotic action in cells [171]. It is therefore classified as a probable noncarcinogen for this project.

Pentane

Although n-pentane is cited as a carcinogen in one reference [6], no primary references could be found to substantiate this allegation in TOXLINE, CANCERLINE, or Reference 5. It is said that aliphatic hydrocarbons may be cocarcinogens [4]. For this project pentane will be considered a noncarcinogen.

Pentachlorophenol

Pentachlorophenol (CAS No. 87-86-5) has been found negative in some relatively short studies on rabbit skin and orally in rats and cats [26]. More recently it has been found negative in two strains of mice both orally and subcutaneously [69]. Pentachlorophenol is also negative in *Drosophila* tests [253], in a host-mediated assay mediated assay in mice [254], and in other microbial systems [152].

Some authors consider pentachlorophenol a known mutagen [255], and there are other positive as well as negative short-term tests reported [18]. It is also positive at the 100-μg level in the hamster embryo adenovirus enchancement assay (personal communication with B. C. Casto on 17 February 1978). For these reasons, pentachlorophenol will be considered a possible carcinogen for this project for the first round of evaluations.

Production and Persistence

One estimate of production is 2.1×10^7 kg (1969 capacity) and a consumption of 2.3×10^7 kg in 1975 [6]. In the soil it degrades completely in >72 days [33]. It has a boiling point of 310°C and a vapor pressure of 1.1×10^{-4} mm at 20°C [33].

---

[253] Vogel, E., and J. L. R. Chandler. Mutagenicity Testing of Cyclamate and Some Pesticides in *Drosophila Melanogaster*. Experientia, 30(6):621-623, 1974.

[254] Buselmaier, W., et al. Comparative Investigations on the Mutagenicity of Pesticides in Mammalian Test Systems. Mutat. Res., 21(1):25-26, 1973.

[255] Daugherty, R. C., and K. Piotrowska. Screening by Negative Chemical Ionization Mass Spectrometry for Environmental Contamination with Toxic Residues: Application to Human Urines. Proc. Natl. Acad. Sci., 73(6):1777-1781, 1976.

Phenol

Phenol (hydroxybenzene, CAS No. 108-95-2) has been reported to give rise to papillomas after administration on mouse skin [153, 256]. Phenol has also been reported negative by injection and negative on the skin of mice [5]. It has recently been given in combination with other chemicals [5]. In mutagenicity tests, phenol has been found to be mutagenic to *Drosophila*, revert *E. coli* to streptomycin independence, and induce chromosome breakage in the root tip of *Allium cepa* while being inactive in reverting *Neurospora crassa* to adenine prototrophy [32]. Phenol is also said to cause second chromosome breaks in *Drosophila* and to cause chromosome breaks in *Vicia* and *Allium sativum*, and it is teratogenic in chickens [44]. One must also remember, however, that normal adults excrete approximately 30 mg of volatile phenols per day in their urine (mainly *p*-cresol and phenol) produced by gut bacterial metabolism of tyrosine [86]. Phenol has tested negative in a micronucleus test [257]. The only positive animal tests were conducted in the fifties with later negative results. The positive *in vitro* tests are with systems which have not been extensively evaluated. Although it is a borderline chemical, phenol will be considered a probable noncarcinogen (with some positive data) for this project.

---

[256] Salaman, M. H., and O. M. Glendenning. Brit. J. Cancer, 11:434-444, 1957.

[257] Hossak, D. J., and J. C. Richardson. Examination of the Potential Mutagenicity of Hair Dye Constituents Using the Micronucleus Test. Experientia, 33(3):377-378, 1977.

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCB, chlorinated diphenyls, Aroclors, Kanechlors) have been cited extensively in the literature as carcinogens [258, 259]. On close inspection, many of the carcinogenicity studies on PCB's have been questionable [5, 260] or negative [261], and the increase in cancer among PCB workers has been questioned [262]. The latest NCI study of PCB's was negative, but they concluded that from the open literature PCB's are probably promoters of carcinogenesis. The PCB's fall on the border between possible and probable carcinogens using the criteria for this project. Because of the positive animal studies [2, 258], they will be classed as a probable carcinogen for this project.

Production and Persistence

It is estimated that 1.8×10^4 kg is emitted per year [1]. Other estimates of production are 1.4×10^7 kg, 2.5×10^6 kg, and 1.8×10^7 kg (1974) [6, 8, 56]. Production of PCB's has been phased out within the last year, so emissions should have dropped to zero. PCB's are essentially nonvolatile, but evaporation to the atmosphere is thought to be important [8]. Reaction with HO radical predicts a half-life of 26 days [56]. PCB's have a boiling point of 365-390°C and a vapor pressure less than 1 mm at 25°C [6].

---

[258] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 261-289.

[259] Lloyd, J. W., et al. Polychlorinated Biphenyls. J. Occup. Med., 18(2):109-113, 1976.

[260] Andrews, E. J., et al. PCB Diet. Science, 180(4083):255-257, 1973.

[261] Ito, N., et al. Histopathological Studies on Liver Tumorigenesis in Rats Treated with Polychlorinated Biphenyls. Gann, 65(6):545-549, 1974.

[262] Lawrence, C. PCB? and Melanoma (letter to the editor). N. Engl. J. Med., 296(2):108-109, 1977.

Propanol

In 1939 and 1940, propanol (propyl alcohol, CAS No. 71-23-8) was found noncarcinogenic in rat feeding studies [222, 223]. The only current references which could be found were Gibel et al. who refer to tumor formation after oral (50 g/kg) and subcutaneous (6 g/kg) administration of propanol to rats [263] and an *E. coli* test [264]. The studies which have been conducted on isopropanol have been negative [265]. Propanol will be considered a probable noncarcinogen (with some significant positive data) for this project.

---

[263] Gibel, W., et al. Experimental Study on Cancerogenic Activity of Propanol-1, 2-Methylpropanol-1, and 3-Methylbutanol. Arch. Geschwulstforsch, 45(1):19-24, 1975.

[264] Gibel, W., et al. Studies on the Toxicity and Mutagenicity of Single Fusel Oil Components on *E. Coli*. Acta Biol. Med. Ger., 23:843-852, 1969.

[265] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 1977. pp. 223-243.

Propylene Oxide

Propylene oxide (methyloxirane, 1,2-epoxypropane; CAS No. 75-56-9) has been reported to cause local sarcomas in a limited number of rats after subcutaneous injection [266]. It was negative in relatively short-term (∿200 days) studies in rats, guinea pigs, rabbits and monkeys given propylene oxide by inhalation [266, 267]. By *in vitro* tests, transformation of hamster cells [96] occurred at 250 mg/ml (personal communication with B. C. Casto on 9 February 1978). It is also reported to cause reversion to adenine, prototrophy in *Neurospora crassa*, and recessive lethal mutation in *Drosophila melanogaster* [32]. For this project it will be considered a possible carcinogen.

Production and Persistence

It is estimated that 4.4 x 10^6 kg propylene oxide is emitted per year [1]. Other production estimates include 7.5 x 10^8 kg per year [6], 8.0 x 10^8 kg (1974) [8], 8.0 x 10^8 kg (1975) [266], and 7.0 x 10^8 kg (1975) [32] with U.S. consumption predicted to grow by 9-10.5% a year from 1975 to 1980 [32]. If dispersed in the atmosphere, epoxides would be oxidized by HO radicals with a half-life of 3-11 hours [8]. The rate constant and half-life for HO radical reaction predict a 23-hour half-life for aliphatic epoxides [32]. Propylene oxide has a boiling point of 33.9°C and a vapor pressure of 596 mm at 25°C [6].

---

[266] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 11, 1976. pp. 191-199.

[267] Rowe, L. K., et al. Toxicity of Propylene Oxide Determined on Experimental Animals. Arch. Industr. Hlth., 13:228-236, 1956.

Pyrene

Pyrene (CAS No. 129-00-0) has generally been tested on mouse skin with negative results [5]. It has also been reported negative on mouse skin followed by croton oil or preceded by benzo(a)pyrene [5]. It is usually considered to be noncarcinogenic [52, 268] and has been reported as nonmutagenic to *S. typhimurium* strains TA 98, 100, 1535 and 1537 [52]. It is considered a noncarcinogen for this project.

---

[268] Arcos, J. C., and M. F. Argus. Chemical Induction of Cancer, Volume IIA, Academic Press, New York, 1974. pp. 210, 237.

Sorbic Acid

Sorbic acid (2,4-hexadienoic acid, CAS No. 110-44-1) is a widely used food preservative. In 1966 and 1968, Dickens et al. reported several rat studies with sorbic acid. In these test (using 6-12 rats) sorbic acid injected subcutaneously at 2 mg/injection in oil or water sometimes caused local fibrosarcomas at the injection site [269-271]. Given in the drinking water at 0.1 g/l, no effects were seen [271]. It is now known that the pH of the injected solution may cause local fibrosarcomas in some strains of rats. In more recent dose response studies, rats [272] and mice [273] (groups of ∿100 animals) were given 0%, 1.5%, or 10% of their diet as sorbic acid with no carcinogenic response. Also sorbic acid with 1,000 ppm parasorbic acid gave no carcinogenic response [274]. Several *in vitro* tests (e.g., *B. subtilis*) have been negative for sorbic acid but positive for reaction products of sorbic acid and sodium nitrite [275]. Better subcutaneous tests should be conducted on sorbic acid, but the negative results on the recent large-scale feeding tests and negative *in vitro* results suggest that sorbic acid should be considered a noncarginogen at the present time.

---

[269] Dickens, F., et al. Brit. J. Cancer, 20:134-144, 1966.

[270] Dickens, F., and H. B. Wayforth. Brit. Emp. Canc. Camp., 46:108, 1968.

[271] Dickens, F., et al. Brit. J. Cancer, 22:762-768, 1968.

[272] Grant, I. F., et al. Long-Term Toxicity of Sorbic Acid in the Rat. Food Cosmet. Toxicol., 13(1):31-45, 1975.

[273] Hendy, R. J., et al. Long-Term Toxicity Studies of Sorbic Acid in Mice. Food Cosmet. Toxicol., 14(5):381-386, 1976.

[274] Mason, P. L., et al. Long-Term Toxicity of Parasorbic Acid in Rats. Food Cosmet. Toxicol., 14(5):387-394, 1976.

[275] Kada, T. Mutagenicity and Carcinogenicity Screening of Food Additives by the Rec-Assay and Reversion Procedures. IARC Sci. Pub. No. 12, 1976. pp. 105-115.

Styrene

Styrene (vinyl benzene, CAS No. 100-42-5) has been found to be both positive [276, 277] and negative [278] on the *S. typhimurium* mutagen test after activation with S-9 microsomes. Without S-9 activation it has been found negative by this test [276, 278]. In other systems, styrene was found positive on a host-mediated forward mutation, gene-conversion yeast system but negative in this system with microsomes only (not host-mediated). It was negative on a Chinese hamster cell test [279], in *Drosophila melanogaster* and *S. pombe* mutation tests [32], and in enhancement of viral transformation tests (personal communication with B. C. Castc on 9 February 1978). It would thus appear that a metabolic product of styrene is a weak mutagen and styrene should probably be considered a possible carcinogen.

Production and Persistence

It is estimated that 5.6 x 10^6 kg styrene is emitted per year from stationary sources [1]. Another source estimates 2.0 x 10^9 kg (1975) produced [6]. It has a 1.28 relative chemical reactivity in the atmosphere (where methane is zero, butane is 1.27, 2-pentane is 1.58 and 2-butene is 15.5) [33, 280]. Styrene has a 145.2°C boiling point and a vapor pressure of 5 mm at 20°C [33].

---

[276] DeMeester, C., et al. Mutagenic Activity of Styrene and Styrene Oxide. Arch. Int. Physiol. Biochim., 85(2):398-399, 1977.

[277] Vainio, H., et al. A Study on the Mutagenic Activity of Styrene and Styrene Oxide. Scand. J. Work Environ. Health, 2(3):147-151, 1976.

[278] Stolz, D. R. Mutagenicity Testing of Styrene and Styrene Epoxide in *Salmonella Typhimurium*. Bull. Environ. Contam. Toxicol., 17(6):739-742, 1977.

[279] Loprieno, N., et al. Mutagenicity of Industrial Compounds: Styrene and Its Possible Metabolite Styrene Oxide. Mutat. Res., 40(4):317-324, 1976.

[280] Yeung, C. K. K., and C. R. Phillips. Estimation of Physiological Smog Sympton Potential from Chemical Reactivity of Hydrocarbons. Atm. Environ., 7, 1973.

Sulfolane

Sulfolane (tetrahydrothiophene-1,1-dioxide, CAS No. 126-33-0) was 1 of the 80 chemicals selected as having the greatest potential environmental effects [7]. Carcinogenicity and mutagenicity were not cited as reasons for its selection. No data could be found in any of the references searched pertaining to mutagenicity or carcinogenicity of this chemical. It is considered a probable noncarcinogen for this project.

Tetrabromoethane

Tetrabromoethane (CAS No. 79-27-6) was 1 of 80 chemicals having potential for environmental effects [56]. It has tested negative in some short-term (92 day), limited-exposure (15 min/day) tests on rats, mice, rabbits and guinea pigs [281]. It has tested positive in an *E. coli* (pol A^+, pol A^-) differential growth mutagen test but negative in *S. typhimurium* strains TA 1530 and TA 1535 [282, 283]. With only one *in vitro* positive test (which has not been extensively validated) tetrabromoethane will be considered a probable noncarcinogen for this project.

---

[281] Gray, A. W. A. Arch. Ind. Hyg., 2:407-419, 1950 (as cited in Reference 5).

[282] Brem, H., et al. The Mutagenicity and DNA-Modifying Effect of Haloalkanes. Cancer Res., 34:2576-2579, 1974.

[283] Rosenkranz, H. S. Mutagenicity and DNA-Modifying Activity: A Comparison of Two Microbial Assays. Mutat. Res., 41(1): 61-70, 1976.

Tetrachloroethane

1,1,2,2-Tetrachloroethane (CAS No. 79-34-5) has been found to be mutagenic in the *S. typhimurium* system for TA 1530 and TA 1535 strains [282]. It has been cited as a carcinogen based on a National Cancer Institute bioassay [284] where it was found to be a carcinogen for mice but not for rats [285]. It is therefore considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 0.4×10^3 kg is emitted per year from stationary sources (in making trichloroethylene from ethylene) [1]. Evaporation of 50% from a 1-ppm solution of water at 25°C will occur in 56 minutes [33]. It has a boiling point of 146.4°C and a vapor pressure of 5 mm at 20°C [33]. Water solubility is 2.9 g/l at 20°C [33].

---

[284] Kraybill, H. F. Origin, Classification, and Distribution of Chemicals in Drinking Water with an Assessment of their Carcinogenic Potential. In: The Environmental Impact of Water Chlorination, National Technical Information Service No. CONF 751096, 1976. p. 229.

[285] Chemical Regulation Reporter, 1(51):1861, 1978.

Reference 286 cites extensive toxicological data but reports no evidence of carcinogenicity, mutagenicity or teratogenicity for tetrachloroethylene (perchloroethylene, CAS No. 127-18-4) in humans. Also no difference in the incidence of tumors was observed between control and experimental rats exposed to 300 or 600 ppm of tetrachloroethylene. A recent report by NCI, however, has shown tetrachloroethylene to be a liver carcinogen in B6C3F1 of both sexes [287]. Tetrachloroethylene has, therefore, been assigned to the probable carcinogen list.

Production and Persistence

It is estimated that 7.8×10^7 kg tetrachloroethylene is emitted per year from stationary sources with solvent evaporation from degreasing operations accounting for better than 99% of that quantity [1]. Other estimates of production are 3.0×10^8 kg (1975) [6], 3.3×10^8 kg produced and 2.6×10^8 kg released [7], and production of 3.3×10^8 kg, 3.1×10^8 kg, and 3.0×10^8 kg in 1974, 1975, and 1976 [32]. A 1976 forecast projected a yearly growth of 3-4% but in light of the NCI carcinogen study, lower standards for occupational exposure from NIOSH, and a decrease in fluorocarbon use, the production of tetrachloroethylene is expected to decrease [32]. It is not photoactive and has an expected HO radical reaction half-life of 8 days [7]. Another reference cites photodegradation with a half-life of 2 days [286]. Evaporation of 50% from a 1-ppm water solution at 27°C will take only 24-28 minutes [33]. It has a boiling point of 121.2°C and a vapor pressure of 14 mm at 20°C [33].

---

[286] Fuller, B. B. Air Pollution Assessment of Tetrachloroethylene. National Technical Information Service No. PB 256 731, 1976. 99 pp.

[287] Bioassay of Tetrachloroethylene for Possible Carcinogenicity, CAS No. 127-18-4. National Technical Information Service No. PB 272 940, 1977.

Tetraethyl Lead

Tetraethyl lead (tetraethyl plumbane, CAS No. 78-00-2) has been found to induce lymphomas when injected subcutaneously into neonatal mice [288] although the significance of this test has been questioned [289]. Oral doses were not found to be teratogenic [290], and an epidemiological study found no health hazard from occupational exposure [291].

Tetraethyl lead has been found to cause DNA fragmentation and to enhance viral transformation in hamster embryo at the 12.5-μg level (personal communication with B. C. Casto on 17 February 1978). Tetraethyl lead is considered a possible carcinogen for this project.

Production and Persistence

One estimate of release to the environment is 1.3×10^8 kg per year [44] from a production of 1.4×10^8 kg. The release figure notes that most of this is through use in gasoline where it is converted to lead halides and some lead phosphates [44]. Another set of figures cites a release of 6.6×10^6 kg from a production of 1.6×10^8 kg in 1973 [6]. The 1971 production has been estimated to be 2.4×10^8 kg []89]. The production of tetraethyl lead is expected to decrease rapidly from these figures because of regulations requiring less lead in gasoline [289]. In the air it has a half-life of 2-3 days from reactions with HO and O_3 radicals [6, 44]. It has a boiling point of 200°C (decomposes) and a vapor pressure of 0.15 mm at 20°C [6, 33].

---

[288] Epstein, S. S., and N. Mantel. Carcinogenicity of Tetraethyl Lead. Experientia, 24(6):580-581, 1968.

[289] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 2, 1973. pp. 150-160.

[290] Kennedy, G. L., et al. Teratogenic Evaluation of Lead Compounds in Mice and Rats. Food Cosmet. Toxicol., 3(6):629-632, 1975.

[291] Robinson, T. R. Health, How Can It Be Measured. In: HEW Publ. (NIOSH) 76-134, 1976. pp. 114-130.

Toluene

An extensive search of CANCERLINE and TOXLINE along with the NTIS document "Air Pollution Assessment of Toluene" [292] and the Stanford Research Institute hazard priority ranking [7] failed to find data which would indicate that toluene is a carcinogen. It tested negative [46] in a differential growth mutagen test using *E. coli* (pol A) and will be considered a noncarcinogen for this project.

---

[292] Walker, P. Air Pollution Assessment of Toluene. National Technical Information Service No. PB 256 735, 1976.

Toluene Diisocyanate

There are no data on TOXLINE or CANCERLINE to indicate that toluene diisocyanate is a mutagen or a carcinogen.

Toluenediamine

Toluenediamine (toluene-2,4-diamine, CAS No. 95-80-7), generally used as a hair dye, has been found by several studies to be non-carcinogenic when applied to the skin of mice [126, 293] and rats [125], although the same data can be interpreted to show increased lung tumors and total tumors in the test groups [294]. Toluenediamine has been reported to produce hepatomas in rats when fed at 0.1% of diet for 35 weeks [295] or 11 g/kg for 36 weeks [296]. In rats, 280 mg/kg (35 weeks) subcutaneously is reported to cause neoplasms [6]. It has also been found to cause morphological transformation in primary Syrian hamster embryo cells. It also mutates *S. typhimurium* strains TA 1538 and TA 98 at 0.5 μg/ml when activated with the S9 microsomes [295, 297]. With positive *in vivo* and *in vitro* tests, toluenediamine will be considered a probable carcinogen for this project.

Production and Persistence

One estimate of production is 2.9 x 10^7 kg per year with 0.015 as a fraction of production loss [6]. It has a boiling point of 292°C and a vapor pressure of 1 mm at 106.5°C [6].

---

[293] Giles, A. L., et al. Dermal Carcinogenicity Study by Mouse-Skin Painting with 2,4-Toluenediamine Alone or in Representative Hair Dye Formulations. J. Toxicol. Environ. Health, 1(3):433-440, 1976.

[294] Bridges, B. A., and M. H. Green. Carcinogenicity of Hair Dyes by Skin Painting in Mice (letter to editor). J. Toxicol. Environ. Health, 2(1):251-252, 1976.

[295] Shah, M. J., et al. Comparative Studies of Bacterial Mutation and Hamster Cell Transformation Induced by 2,4-Toluenediamine (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:22, 1977.

[296] Cancer Research, 29:1137, 1969.

[297] Pienta, R. J., et al. Correlation of Bacterial Mutagenicity and Hamster Cell Transformations with Tumorigenicity Induced by 2,4-Toluenediamine. Cancer Lett. (Amsterdam), 3(1/2): 45-52, 1977.

Toxaphene

No significant data were found to indicate that toxaphene is a mutagen or a carcinogen. It tests negative on the dominant lethal test for mice [30]. It has been placed on the probable noncarcinogen list for this project.

Trichlorfon

Trichlorfon has been found to be carcinogenic to mice, rats, and cats given orally, subcutaneously, cutaneously, or intermuscularly [3, 5]. It has also been found to be mutagenic by at least five different test systems [3, 5]. It is, therefore, to be considered a probable carcinogen.

Production and Persistence

It is estimated that 100 kg/year of trichlorfon is emitted from stationary sources [1].

Trichloroethane

A National Cancer Institute bioassay of 1,1,1-trichloroethane found no correlation between this chemical and any cancers which developed in the control versus the test rats and mice [298]. It was negative on an enhancement of viral transformation test (personal communication with B. C. Casto on 9 February 1978). It has been placed on the noncarcinogen list for this project.

---

[298] Bioassay of 1,1,1-Trichloroethane for Possible Carcinogenicity. Carcinog. Tech. Rep. Serv. - Natl. Cancer Inst. (U.S.); ISS NCI-CG-TR-3, 1975. 70 pp.

Trichloroethylene

Trichloroethylene (trichloroethene, TCE; CAS No. 79-01-6) has been found to induce a high incidence of hepatocellular carcinoma in B6C3F1 mice of both sexes by NCI [299]. It has also been found to be weakly mutagenic in *E. coli* and to the TA 100 strain of *S. typhimurium* (0.8-2.0% vapor dose response when exposed 1 hour) in the presence of activated microsomes [32]. A review of the production, uses and environmental effects has been compiled by Fishbein [75]. TCE is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1.6 x 10^8 kg of TCE is emitted per year with 95% of that coming from solvent evaporation in degreasing operations [1]. Another estimate is a production of 1.93 x 10^8 kg with 1.95 x 10^8 kg released [7]. Other production estimates [6, 8] include 1.8 x 10^8 kg (1974) and 1.3 x 10^8 kg/year, with about 60% of the production released to the environment [300]. Production has also been reported to be 1.8 x 10^8 kg (1974), 1.3 x 10^8 (1975) and 1.4 x 10^8 kg (1976) with a 1% decline predicted for future years [32]. Since that prediction, OSHA has lowered the standard for occupational exposure and NCI found that TCE causes tumors in mice which will mean a much greater decline in the expected production [32]. TCE has a high atmospheric photodegradation rate with a half-life of 0.3 day at sea level [300]. Other sources predict atmospheric reaction with the HO radical with a half-life of 36 hours [8] or less than 50 hours [7]. With its high volatility and low water solubility it is expected to fairly rapidly migrate into the atmosphere. In fact 50% of a 1-ppm solution will evaporate from water at 25°C in 19-24 minutes [33]. Its boiling point is 86.7°C and it has a vapor pressure of 60 mm at 20°C [33].

---

[299] Carcinogenesis Bioassay of Trichloroethylene, CAS No. 79-01-6. National Cancer Institute Carcinogenesis Technical Report Services, Number 2, February 1976 (NCI-CG-TR-2).

[300] Fuller, B. B. Air Pollution Assessment of Trichloroethylene. National Technical Information Service No. PB 256 730, 1976.

Trichlorofluoromethane

In mice, trichlorofluoromethane (Freon-11, F-11) in combination with the insecticidal synergist piperonyl butoxide increased the incidence of malignant hepatomas while Freon-11 by itself was found to be noncarcinogenic [301]. No other carcinogenic data were found on Freon-11, and it has been found to be nonmutagenic in *S. typhimurium* tests with and without microsomal activation [302]. Preliminary results from an NCI bioassay show no difference between control and treated male or female rats [303]. It is probably not a carcinogen.

---

[301] Epstein, S. S., et al. Synergistic Toxicity and Carcinogenicity of "Freons" and Piperonyl Butoxide. Nature, 214: 526-528, 1967.

[302] Uehleke, H., et al. Metabolic Activation of Haloalkanes and Tests *in Vitro* for Mutagenicity. Xenobiotica, 7(7): 393-400, 1977.

[303] NCI Preliminary data on trichlorofluoromethane, Nov. 27, 1976.

Trichlorophenol

Trichlorophenol (2,4,6-trichlorophenol, Dowicide 2S; CAS No. 88-06-2) has been found to be a carcinogen in mice when given orally but not subcutaneously [69, 77]. Seven/seventy-two hepatomas, 6/72 pulmonary adenomas, and 7/72 reticulum cell sarcomas were found. (2,4,5-Trichlorophenol was only evaluated by the subcutaneous route [69] and was found negative by this route of administration, as was 2,4,6-trichlorophenol.) Trichlorophenol may cause abnormal pollen in broad bean plants [304]. No other pertinent literature references were found on TOXLINE or CANCERLINE to substantiate or refute the carcinogenic potential of trichlorophenol. It has been placed on the possible carcinogen list for this project.

Production and Persistence

It is estimated that 5 x 10^2 kg trichlorophenol is emitted from stationary sources per year [1]. Since this is used as a pesticide, nonstationary sources (or total production) should be considered. It completely disappears in soil suspensions in 5 days [33]. Trichlorophenol (2,4,6) has a boiling point of 244.5°C and a solubility of 800 mg/l at 25°C [33].

---

[304] Cytological Effects of Pesticides. V. Effects of Some Herbicides on *Vicia Faba*. Cytologia, 39(4):663-643, 1974.

Urethane[a]

Urethane (ethyl carbamate, CAS No. 51-79-6) has been shown to be carcinogenic in mice, rats and hamsters following administration by the oral, inhalation, subcutaneous or intraperitoneal routes [305]. It generally causes lung tumors, lymphomas, hepatomas, melanomas, and vascular tumors. With all of these positive data, urethane is considered a probable carcinogen for this project.

Production and Persistence

The only production data which could be found cited from one U.S. producing company with no data given and production below 454 kg from a second company [305]. It has a boiling point of 183°C, sublimes at 102°C and 54 mm Hg, and is volatile at room temperature [305].

---

[a] The name urethane is sometimes applied to high molecular weight polyurethanes used as foams, elastomers and coatings. Such products are not made from the chemical urethane and do not generate it on decomposition.

- - - - - - - - - - -

[305] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 111-140.

Vinyl Acetate

Vinyl acetate (CAS No. 108-05-4) has been found to be noncarcinogenic in rats at 2,500 ppm for 4 hr/day for 12 months by C. Maltoni [5]. It has also been found negative on mouse skin [306], mouse sebaceous glands [307], and *S. typhimurium* tests [52, 97, 146]. Both commercial vinyl acetate [96] and repeated tests of purified vinyl acetate (personal communication with B. C. Casto on 9 February 1978) have been found to be mutagenic at a level of 150 μg/ml in viral transformation of Syrian hamster cells. Because of this enhanced transformation, vinyl acetate will be considered a possible carcinogen for this project for the first round of evaluations.

Production and Persistence

It is estimated that 6.8×10^5 kg is emitted per year from stationary sources [1]. Another estimate is a release of 7.8×10^6 kg from a production of 5.5×10^8 kg [6]. It reacts with oxidizing materials in the atmosphere [6], and has a boiling point of 73°C and a vapor pressure of 83 mm at 20°C [33].

---

[306] Garibyan, D. K., and S. A. Papoyan. Study of the Blastomogenic Activity of Certain Chemical Substances Using a High-Speed Test Method. Gig. Sanit., 8:74-76, 1977.

[307] Garibyan, D. K., and S. A. Papoyan. Use of Sebaceous Gland Reactions as a Test for Rapid Determination of Carcinogenic Activity of Chemicals. Nekot. Itogi Izuch. Zagryazneniya Vnesh. Sredy Kanstserogen. Veschestoami; 112-115, 1972.

Vinyl Bromide

Vinyl bromide (bromoethylene, CAS No. 593-60-2) has not been tested very much. It was not found in Reference 5, and from CANCERLINE and TOXLINE only one author has conducted *in vitro* tests on it. In this test, *S. typhimurium* strain TA 100 was found to give a dose-response mutation frequency of 26 and 9 revertants per micromole per hour with and without the S9 liver microsome fraction [146]. It was also found that liver fractions from human biopsies converted vinyl bromide to more mutagenic compounds. Another study by the same authors demonstrated that vinyl bromide is activated by the liver homogenates in the same manner as is vinyl chloride [308]. Although there is not much information on which to base any decision, vinyl bromide will be considered a possible carcinogen for the first phase of this project.

Production and Persistence

It is estimated that 4 x 10^3 kg/year of vinyl bromide is emitted from stationary sources [1].

---

[308] Barbin, A., et al. Liver-Microsome-Mediated Formation of Alkylating Agents from Vinyl Bromide and Vinyl Chloride. Biochem. Biophys. Res. Comm., 67(2):596-603, 1975.

Vinyl Chloride

Vinyl chloride (CAS No. 75-01-4) has been found to cause lung tumors, mammary carcinomas and angiosarcomas in mice following exposure by inhalation [309]. Similar exposure for rats produces angiosarcomas of the liver and other organs, zymbal gland carcinomas, and nephroblastomas [309]. In view of the extreme rarity of angiosarcoma of the liver in the general population, 16 cases in vinyl chloride workers is evidence of a causal relationship. It has also been found to be a mutagen of *S. typhimurium* (Ames test [97] and in enhancement of viral transformation (personal communication with B. C. Casto on 9 February 1978).

Production and Persistence

It is estimated that 1.4 x 10^8 kg is emitted per [1]. The 1973 production of vinyl chloride was 2.4 x 10^9 g in the United States, of which 97% was used for production of polyvinyl chloride [309]. A 1974 EPA estimate was 9 x 10^7 kg released to the atmosphere [309]. Other estimates of production are 2.5 x 10^9 kg (1974) [8] and 2.5 x 10^9 kg, 1.9 x 10^9 kg and 2.6 x 10^9 kg in 1974, 1975, and 1976 [32]. The demand for PVC is expected to increase at an annual rate of 8-10% through 1981 [32]. In the atmosphere it reacts with the HO radical with a 12-hour half-life [8]. It has a boiling point of -14°C and a vapor pressure of 2,660 mm at 25°C [33].

---

[309] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 7, 1974. pp. 291-305.

Vinylidene Chloride

Vinylidene chloride (1,1-dichloroethylene, CAS No. 75-35-4) has been found to be mutagenic in the *S. typhimurium* test [97, 146, 310] and in a metabolizing *in vitro* system with *E. coli* K12 [311]. It has also been reported to be carcinogenic in rats and rabbits [312], and in preliminary studies 200 ppm were carcinogenic to rats and mice by inhalation [313]. On reference concludes that airborne emissions of vinylidene chloride are not likely to pose a significant risk to the general population [314]. Vinylidene chloride has been placed on the probable carcinogen list for this project.

Production and Persistence

It is estimated that 2.1 x 10^5 kg are emitted a year from stationary sources, with 70% of this coming from the oxychlorination of ethylene dichloride [1]. Other estimates of production and release are production of 2.7 x 10^7 kg with 4.1 x 10^5 kg released [7], production of 1.2 x 10^8 kg with 1.4-1.8 x 10^6 kg emitted and a 5-10% growth rate predicted [314], 1.2 x 10^8 kg produced with 1.1 x 10^6 kg released [6], 7.7 x 10^7 kg produced from 1973 to 1975 with a 7% growth predicted [32], and 2.7 x 10^7 kg produced in 1972 [8]. The O_3 and HO reactions are estimated to give less than a 1-day half-life [6], while another reference cites HO half-life of 26 hours [8]. Evaporation of 50% from a 1-ppm solution at 25°C will occur in 22 minutes [33]. It has a vapor pressure of 617 mm at 25°C and a boiling point of 37°C [6].

---

[310] IARC Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity. International Agency for Research on Cancer, Lyon, Bulletin No. 5, July 1975.

[311] Greim, H. G., et al. Mutagenicity *in Vitro* and Potential Carcinogenicity of Chlorinated Ethylenes as a Function of Metabolic Oxirane Formation. Biochem. Pharmacol., 24:2013-2017, 1975.

[312] Food Additives, Packaging Material for Use During Irradiation of Pre-Packaged Foods. Fed. Register, 33:4569, 1968.

[313] Caputo, A., et al. Oncogenicity of Vinyl Chloride at Low Concentrations in Rats and Rabbits. IRCS, 2:1582, 1974.

[314] Hushon, J., and M. Kornreich. Air Pollution Assessment of Vinylidene Chloride. National Technical Information Service No. PB 256 738, 1976.

Xylene

Some literature suggests that xylenes are noncarcinogenic irritants [315, 316]. Other literature indicates that all of the xylenes cause neoplasms on mice after dermal application [6]. This may refer to the same study where an increased number of unspecified tumors were observed in the mouse upon dermal application of mixed xylene after the use of croton oil or methane [7]. The results of this study are considered equivocal [7] and would at most suggest that xylenes are promoters. The old xylene carcinogen literature is negative after skin painting mice [5], and xylene is considered a noncarcinogen for this project.

---

[315] Pound, A. W. Induced Cell Proliferation and the Initiation of Skin Tumor Formation in Mice by Ultraviolet Light. Pathology, 2(4):269-275, 1970.

[316] Listgarten, M. A., et al. Ultrastructural Alterations in Hamster Cheek Pouch Epithelium in Response to a Carcinogen. Arch. Oral Biol., 8(2):145-165, 1963.

APPENDIX B

A REVIEW OF THE CARCINOGEN COFACTOR LITERATURE

INTRODUCTION

This appendix presents the state-of-the-art review of the carcinogen cofactor literature that was performed as part of the first year's effort on this contract. Primary emphasis is given to industrial chemicals and the effects of cofactors on the carcinogenic potential of these chemicals.

The information presented is derived from more than 2,300 literature citations (most included abstracts) accessed from CANCERLINE, TOXLINE, MEDLINE, CANCERPROJ, AND CHEMCON searched through the National Library of Medicine and Systems Development Corporation.

Some of the keywords or word stems* utilized in the computer search were carcinogen..., cocarcinogen..., and syncarcinogen.... Other words used in conjunction with carcinogen... included: modifier(s), promoter(s), inhibitor(s), enhancer(s), synergy, and synergism. This review attempts to summarize some of the significant findings reported in the multitude of literature found on this subject.

BACKGROUND

Chemically induced carcinogenesis in man is rapidly becoming one of the greatest concerns of society. Statistical data on the incidence of cancer in humans and laboratory testing on animals have indicated that a wide variety of chemical compounds are responsible at least in part for many of the various forms of human cancer. These substances traverse a number of interfaces and enter or contact the human body through media such as air, food, water, physical contact, and medication. In addition these substances can undergo various changes at each interface, within the media of transport, or within the human receptor. Noncarcinogenic substances when metabolized by the body have been found to produce carcinogenic byproducts.

---

*The word stems and all terms beginning with them (indicated by ...) were searched.

There are various theories on the mechanism of carcinogenesis; the more generally accepted is that of a biphasic response of initiation and promotion. Promotion implies a latent period after initiation of a target receptor. This also implies that the system or mechanism can be inactivated or inhibited. In conjunction with this theory many carcinogenic and noncarcinogenic compounds or their metabolites have been found to interact with other chemicals or agents to enhance or inhibit carcinogenic activity. This modification can take place by preliminary, simultaneous, or subsequent contact of each substance with the target receptor.

Obviously a complete characterization of the interaction of chemical substances in human carcinogenesis is a monumental task because chemicals that are carcinogenic or are cofactors of potential carcinogens exist simultaneously in the various spheres of our environment and may act to inhibit or enhance other carcinogenic activity in varying degrees. This review presents the findings of various researchers in the area of carcinogenic cofactors; it identifies each substance, its method of interaction, the human organs it affects, and its sphere of transport and entry into the human body.

Apparently the terminology in the area of carcinogenic cofactors has not been standardized or widely accepted, and terms such as cocarcinogen, syncarcinogen, promoter, and enhancer are sometimes used interchangeably. According to Hecker [317] the divergent use of terminology in carcinogenesis has created a great deal of confusion in tumor etiology. Hecker attempts to standardize these terms as follows:

Solitary carcinogens: first order carcinogenic risk factors. The most simple toxicologic process of manifestation of their carcinogenic effect is unifactorial exposure of the target tissue.

Syncarcinogenesis: generation of neoplasia caused by multifactorial exposure to the target tissue. Exposure to a submanifestational dose of a solitary carcinogen [i.e., benzo(a)pyrene] may induce a distinct inclination to cancer, while a subsequent exposure to either a solitary carcinogen or to a cocarcinogen may augment the irreversible effects caused by the initial exposure. When exposure is to more than one solitary carcinogen, it is sometimes called pluricarcinogenesis.

---

[317] Hecker, E. Definitions and Terminology in Carcinogenesis - Analyses and Proposals (Meeting Abstract). Third International Symposium on Detection and Prevention of Cancer, 1976. p. 67.

Cocarcinogenesis: exposure to a submanifestational dose of the solitary carcinogen followed by exposure to a cocarcinogen which alone does not produce tumors or cancer.

Other terms frequently employed are:

Promoters: agents that interact with membranes, stimulate and alter genetic expression, and increase cell proliferation rate. Promotion, unlike initiation, is reversible, and the promoting agents must be applied repeatedly before tumors are formed [318].

Enhancement: this term is often used to describe synergistic effects of chemical agents. Usually when the chemical agent tested increases the incidence of cancer cells or decreases the response time of cancer manifestation over that of the known carcinogen, it is said to enhance carcinogenic activity.

Inhibitors: agents that block or retard the carcinogenic activity of a known carcinogen. Also called anticarcinogens.

Discussion of carcinogenic cofactors is presented by the basic means of human exposure, that is, dietary cofactors, physical agents and body materials, therapeutic agents and treatments, environmental cofactors, and industrial chemicals and pollutants. Some carcinogenic cofactors exist in several spheres and can be introduced to the body in various forms. In addition, certain cofactors have demonstrated both synergistic and inhibitory activity. These overlaps and contradictions are addressed in the review.

DIETARY COFACTORS

Dietary cofactors are those agents which are taken internally as part of routine dietary intake, or in some form supplement the diet, which if present or absent affect carcinogenic activity. Included in this category are dietary related agents such as cooking aerosols.

In laboratory studies on rats [319] fed diets deficient in lipotropes (choline, methionine, folic acid), amino acids, and niacin, and high in fat, liver cancer induced by several carcinogens was enhanced. This is shown again for amino acids in another study [320]. The addition of beef fat to an adequate diet did not enhance tumer induction. Methionine, contained in both the amino acid and lipotrope supplement, was postulated to have inhibitory effect which has also been reported to be found in other studies. The principal carcinogen used in this study was N-nitrosodiethylamine. The protein amino acid L-cysteine has been found to also inhibit cigarette smoke induced cancer [321], while other amino acids such as DL-ethionine have been demonstrated to accelerate chemically induced carcinogenesis in animal tests [322, 323]. DL-tryptophan, another common dietary component, has been tested in several studies, all of which demonstrated promotion of chemically induced carcinogenesis in animals [324-326]. Another study of dietary components was performed [327] which showed that colon tumor induction is increased by increased dietary fat intake or dietary deficiency of vitamin A. The enhancing effect was augmented by lipotrope deficiency. A survey of 8,278 Norwegian men resulted in findings which suggest that vitamin A active compounds inhibit pulmonary carcinogenesis in man [328].

---

[318] Yuspa, S. H., et al. Cutaneous Chemical Carcinogenesis: Past, Present, and Future. J. Invest. Dermatol., 67(1): 199-208, 1976.

[319] Rogers, A. E. Reduction of n-Nitrosodiethylamine Carcinogenesis in Rats by Lipotrope or Amino Acid Supplementation of a Marginally Deficient Diet. Cancer Res., 37(1):194-199, 1977.

---

[320] Syrotuck, J. A., and B. S. Worthington. Nutritional Effects on Syngeneic Tumor Immunity and Carcinogenesis in Mice, I. Selected Essential Amino Acids (Meeting Abstract). Fed. Proc., 36(3):1163, 1977.

[321] Leuchtenberger, C., and R. Leuchtenberger. Protection of Hamster Lung Cultures by L-Cysteine Against Carcinogenic Effects of Fresh Smoke from Tobacco or Marihauana Cigarettes (Meeting Abstract). J. Cell. Biol., 70(2/Part 2): 44a, 1976.

[322] Takamiua, K., et al. Effect of Phenobarbital and DL-Ethionine on 4-(Dimethylamino)azobenzene-Metabolizing Enzymes and Carcinogenesis. Gann, 64(4):363-372, 1973.

[323] Ito, N., et al. The Development of Carcinoma in Liver of Rats Treated with *m*-Toluylenediamine and the Synergistic and Antagonistic Effects with Other Chemicals. Cancer Res., 29(5):1137-1145, 1969.

[324] Radomski, J. L., et al. Cocarcinogenic Interaction Between D,L-Tryptophan and 4-Aminobiphenyl or 2-Naphthylamine in Dogs. J. Natl. Cancer Inst., 58(6):1831-1834, 1977.

[325] Ito, N., et al. Effect of Various Carcinogenic and Non-carcinogenic Substances on Development of Bladder Tumors in Rats Induced by n-Butyl-N-(4-hydroxybutyl)nitrosoamine. Gann, 65(2):123-130, 1974.

[326] Matsushima, M. The Role of the Promoter L-Tryptophan on Tumorigenesis in the Urinary Bladder. 2. Urinary Bladder Carcinogenicity of FANFT (Initiating Factor) and L-Tryptophan (Promoting Factor) in Mice. Jpn. J. Urol., 68(8):731-736, 1977.

[327] Rogers, A. E., and P. M. Newberne. Dietary Effects on Chemical Carcinogenesis in Animal Models for Colon and Liver Tumors. Cancer Res., 35(11/Part 2):3427-3431, 1975.

Vitamin A in conjunction with Fluorouracil has been shown to inhibit 7,12-dimethylbenzanthracene (DMBA) induced skin tumors in rabbits [329]. Vitamin B2 deficiency and hepatic injury resulting from inadequate food intake have been postulated to promote liver cancer [330]. However, nicotinamide, a B vitamin, has been shown in animal tests to promote the development of kidney neoplasms and increase the incidence of pancreatic tumors. It was also suggested that it may offer some protection against the acute effects of liver cancer but not against tumor induction [331].

Studies have shown that synthetic inducers of increased microsomal mixed function oxidase activity may inhibit the neoplastic effect of chemical carcinogens [332]. An increasing number of these substances are being found in natural products. Cruciferous vegetables including brussels sprouts, cabbage, and cauliflower have been found to contain indole-3-acetonitrile, indole-3-carbinol, and 3,3'-diindolymethane which have been identified as inducers of oxidase activity, or potential carcinogenic inhibitors.

Another category of dietary inhibitors comprises the antioxidants. Several of these compounds have been found to inhibit the carcinogenic effects of a variety of chemical carcinogens in animal tests. Considerable work has been done with butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), phenolic antioxidants extensively used as food additives. In studies [333] where BHA and BHT were added to the diet of mice with benzo(a)pyrene [B(a)P] it was found that either antioxidant inhibited carcinogenesis. Other antioxidants having carcinogenic inhibiting capabilities include dimethylhydrazine, tetraethylthiuram disulfide, ethoxyquin, disulfiram, dimethyldithiocarbamate, 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (commerical animal food additive), cysteamine, benzyl isothiocyanate and benzyl thiocyanate (naturally occurring antioxidants), sodium selenide, and α-tocophenol [330, 332, 333]. Large quantities of salt may enhance the action of gastrocarcinogens such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) [330].

---

[328] Bjelke, E. Dietary Vitamin A and Human Lung Cancer. Int. J. Cancer, 15(4):561-565, 1975.

[329] Prutkin, L. Inhibition of Tumorigenesis by Topical Application of Low Doses of Vitamin A Acid and Fluorouracil. Experientia, 31(4):494, 1975.

[330] Sugimura, T. Carcinogens in Foods and Food Products. Proceedings of the Eleventh Canadian Cancer Research Conference, Natl. Cancer Inst. Canada, Toronto, Ontario, 6-8 May 1976, 1976.

[331] Schoental, R. The Role of Nicotinamide and of Certain Other Modifying Factors in Diethylnitrosamine Carcinogenesis: Fusaria Mycotoxins and "Spontaneous" Tumors in Animals and Man. Cancer (Suppl.), 40(4):1835-1840, 1977.

[332] Wattenberg, L. W. et al. Dietary Constituents Altering the Response to Chemical Carcinogens. Fed. Proc., 35:1327-1331, 1976.

The artificial sweeteners saccharin and cyclamates have been shown to act as cocarcinogens with subcarcinogenic doses of N-methyl-N-nitrosourea, a strong bladder carcinogen, when tested on rats [334, 335]. Another study on mice, however, concluded that these artificial sweeteners had no carcinogenic or cocarcinogenic activity under the experimental conditions [336].

Coffee has been shown to contain constituents of which some have been shown to promote and others to inhibit carcinogenesis. Caffeine has been tested on mice as a post treatment to exposure to 4-nitroquinoline-1-oxide (4NQO), a known carcinogen, and showed inhibitory properties [337]. In contrast chlorogenic acid (13% of the soluble constituent of coffee) has been shown to be a very powerful catalyst for N-nitrosoamine formation in the digestive tract [338]. Tests conducted on mice indicate that neutral sterols (cholesterol, caprostanol, and caprostanone) are moderately inhibitory on B(a)P carcinogenesis [339]. However, other researchers have found cholesterol to promote carcinogenesis which was previously inhibited by phospholipids [340].

---

[333] Wattenberg, L. W. Inhibition of Chemical Carcinogenesis by Antioxidants and Some Additional Compounds. In: Fundamentals in Cancer Prevention, Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, Japan, 1976. pp. 153-166.

[334] Chowaniec, J., et al. Histology of Tumour Formation in the Bladder of Rats Receiving Dietary Saccharin and a Single Dose of n-Methyl n-Nitrosourea (Meeting Abstract). B. J. Cancer, 29(1):93, 1974.

[335] Hicks, R. M., and J. Chowaniec. The Importance of Synergy Between Weak Carcinogens in the Induction of Bladder Cancer in Experimental Animals and Humans. Cancer Res., 37(8, Part 2):2943-2949, 1977.

[336] Roe, F. J., et al. Feeding Studies on Sodium Cyclamate, Saccharin and Sucrose for Carcinogenic and Tumour-Promoting Activity. Food Cosmet. Toxicol., 8(2):135-145, 1970.

[337] Nomura, T. Inhibitory Effect of Caffeine on Chemical Carcinogenesis in Mice (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:244, 1977.

Nitrosoamines, known to have carcinogenic activity, have been shown to act synergistically with B(a)P, resulting in a higher incidence of lung and stomach tumors in animals than if each agent were administered separately [341]. Nitrosoamines may not enter the human body as such but can be formed through metabolic processes and altered by other agents. For instance, nitrites can react with secondary amines to yield nitrosoamines, and substances such as gallic acid and 4-methylcatechol (in coffee) enhance formation of nitrosoamines, whereas ascorbic acid depresses formation of nitrosoamines [330]. Dietary sodium sulfate has been shown to enhance azo dye carcinogenesis [342].

Many major constituents of essential oils, flavors, and spices are also considered tumor promoting and carcinogenic. The major constituent of orange oil, D-limonene, is a skin tumor promoting agent in mice, while turpentine oil and eucalyptus oil contain the cocarcinogens L-pinene and phellandrene. Other essential oils with lower terpene levels have less tumor promoting activity [343]. Citrus oils and croton oil have been found to be cocarcinogenic [344, 345].

---

[338] Challis, B. C., and C. D. Bartlett. Possible Cocarcinogenic Effects of Coffee Constitutents. Nature (Lond.), 254(5500): 532-533, 1975.

[339] Watanabe, K., et al. Effect of Bile Acids and Neutral Sterols on Benzo(a)pyrene-Induced Tumorigenesis in Skin of Mice: Brief Communication. J. Natl. Cancer Inst., 60(6): 1501-1503, 1978.

[340] Altman, R. F., et al. Phospholipids Retard and Cholesterol Promotes the Formation of Tumours Induced by Carcinogenic Hydrocarbons. Z. Naturforsch. (B), 23(9):1277-1279, 1968.

[341] Bingham, E., et al. Multiple Factors in Carcinogenesis. Ann. N.Y. Acad. Sci., 271:14-21, 1976.

[342] Blunck, J. M., and C. E. Crowther. Enhancement of Azo Dye Carcinogenesis by Dietary Sodium Sulphate. Eur. J. Cancer, 11(1):23-31, 1975.

Studies indicating that certain cooking oils possess cocarcinogenic activity have been reported since 1964. Triolein, a major constituent of cottonseed oil and sesame oil, was tested on mice and was found to be cocarcinogenic [346, 347].

Tests with butter oil and sunflower oil have demonstrated that, when overheated, these oils possess carcinogenic and cocarcinogenic properties [348]. Studies using a mutant safflower oil rich in oleic acid indicate that polyunsaturated fats act as cocarcinogens [349]. Cyclopropenoid fatty acids (CPFA) (e.g., sterculic acid and malvalic acid) occur in certain foodstuffs such as cottonseed oil, kapok oil, and flour and have been demonstrated to act as powerful tumor promoters or cocarcinogens for aflatoxin induced liver cancer in trout [350-352]. Because it has been suggested that the high incidence of colon cancer in man is due to lack of dietary fiber, studies were conducted on rats using wheat bran, pectin, alfalfa, and carrageenin. Fifteen percent dietary carrageenin promoted colon tumors, and the modifying effect of dietary fibers depended on the type of fiber used [353].

---

[343] Homburger, F., and E. Boger. The Carcinogenicity of Essential Oils, Flavors, and Spices: A Review. Cancer Res., 28(11):2372-2374, 1968.

[344] Salaman, M. H., and F. J. Roe. Cocarcinogenesis. Br. Med. Bull., 20(2):139-144, 1964.

[345] Schramm, R., and W. Gibel. Carcinogenic and Cocarcinogenic Plant Products, II. Carcinogenic Substances Synthesized by Pteridophyta (Filicinae) and Spermatophyta (Cyadineae, Dicotyledoneae, Monocotyledoneae). Arch. Geschwulstforsch., 33(2):169-188, 1969.

[346] Zschiesche, W., and G. Bruns. Carcinogenesis of 7-Ketocholesterol. Oncology, 18(4):289-299, 1964.

[347] Bryson, G., and F. Bischoff. Triolein as a Cocarcinogen. Fed. Proc., 23(2, Pt. 1):106, 1964.

[348] Dzagnidze, L. I., and P. N. Krasniyanskaya. A Study of Possible Carcinogenic and Cocarcinogeni Properties of Overheated Oils. Soobshch. Akad. Nauk. Gruz. SSR, 67(1): 229-231, 1972.

[349] Dayton, S., et al. Effect of High-Oleic and High-Linoleic Safflower Oils on Mammary Tumors Induced in Rates by 7,12-Dimethylbenz(alpha)anthracene. J. Nutr., 107(8):1353-1360, August 1977.

A study of furfural on the respiratory tract of hamsters suggests it is a cocarcinogenic agent with B(a)P [354]. Furfural can be found in cigarette smoke but also in foodstuffs including bread, coffee, processed fruits and juices, and alcoholic beverages. This may be supported by a study which showed that extracts from dried plums showed cocarcinogenic activity [355].

Although alcohol is not part of what is considered a normal diet, alcoholic beverages are consumed by many people. It is estimated that alcohol plays an etiological role in greater than 50% of the oropharyngeal cancers in the United States [356].

---

[350] Sinnhuber, R., O., et al. Metabolism and Cocarcinogenicity of Cyclopropenes. Oregon State Higher Educ. Sys., School of Agriculture, Food Science and Technology, Corvallis, Oregon.

[351] Lee, D. J., et al. Synergism Between Cyclopropenoid Fatty Acids and Chemical Carcinogens in Rainbow Trout (Salmo Gairdneri). Cancer Res., 28(11):2312-2318, 1968.

[352] Petering, H. D. Diet, Nutrition, and Cancer. Adv. Exp. Med. Biol., 91:207-228, 1977.

[353] Raikow, R. B. Effects of Carcinogens or Suspected Carcinogens on Viral Luekemogenesis in C57BL/10, SJL/J Mice and Their F1 Hybrid (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 19:23, 1978.

[354] Rick, E. W. Furfural: Exogenous Precursor of Certain Urinary Furans and Possible Toxicologic Agent in Humans. Clin. Chem., 18(12):1550-1551, 1972.

[355] Ruchkovskii, B. S., et al. Carcinogenic and Cocarcinogenic Action of Dried Fruit Extract. Vopr. Onkol., 20(4):58-61, 1974.

[356] Rothman, K. J. The Effect of Alcohol Consumption on Risk of Cancer of the Head and Neck. (Head and Neck Cancer, State-of-the-Art Conference, St. Louis, MO., February 16-18, 1976.) Laryngoscope, 88(1, Part 2, Suppl. 8):51-55, 1978.

An investigation of the incidence of oral cancer in women who smoke and drink indicates that alcohol is a cocarcinogen with cigarette smoke [357]. This is also suggested in another study [358]. Another study performed on rats suggests a synergism between inhaled vinyl chloride and ingested alcohol in tumorigenesis [359].

Investigations of the effect of masticatory substances such as chewing tobacco and betel nuts have indicated that in conjunction with tobacco smoke these substances may be cocarcinogens [360, 361].

PHYSICAL AGENTS AND BODY MATERIALS

Physical agents which act as carcinogenic cofactors are generally those which act upon or contact the human body but usually are not chemical in nature, such as forces or forms of energy (x-rays). Body materials are those which relate to body chemistry or body functions.

The tissues in the human oral cavity are generally exposed to repeated low doses of x-rays from diagnostic medical and dental radiology. Studies have been performed on hamster cells and hamster cheek pounch where repeated low doses of x-rays have exhibited carcinogenic or tumor promoting activity with repeated low doses of a known carcinogen (DMBA) or where x-ray treatment preceded administration of the carcinogenic agent [362, 363]. The cofactor effect of ultraviolet (UV) light is not quite as well defined. A study of the effect of UV light exposure to hamster cells followed by B(a)P or N-acetoxyfluorenyl-acetamide resulted in neither an additive nor synergistic enhancement observed with either chemical agent alone [363]. However, another study showed significant enhancement by UV light on DMBA initiated skin carcinogenesis [329]. The explanation appears to be in the sequence of exposure. An additional study on nonhuman primates demonstrated that DMBA was oncogenic when applied to the skin in combination with UV light [364].

---

[357] Bross, I. D., and J. Coombs. Early Onset of Oral Cancer Among Women Who Smoke and Drink. Proc. Am. Assoc. Cancer Res., 17:1, 1976.

[358] Gibel, W., and G. Wittig. On the Experimental Induction of Carcinoma of the Esophagus. Dtsch. Gesundheitsw., 19(14): 635-637, 1964.

[359] Radike, M. J., et al. Effect of Ethanol and Vinyl Chloride on the Induction of Liver Tumors: Preliminary Report. Environ. Health Perspect., 21:153-155, 1977.

[360] Jayant, K. Statistical Appraisal of the Association of Smoking and Chewing Habits to Oral and Pharyngeal Cancers. Indian J. Cancer, 14(4):293-299, 1977.

[361] Ranadive, K. J., et al. Experimental Studies on Betel Nut and Tobacco Carcinogenicity. Int. J. Cancer, 17(4):469-476, 15 April 1976.

Removal of the gall bladder (cholecystectomy) has been suggested in several studies to have a cocarcinogenic effect in cancer of the colon. A detailed investigation of 760 cases of large bowel cancer revealed a strong associate between cholecystectomy and ascending colon cancer [365].

An experimental study on mice was initiated when another group of researchers showed clinical findings that 10% of patients with carcinoma of the large bowel had previous cholecystectomies. This cocarcinogenic effect was verified in the animal tests with the carcinogen 1,2-dimethylhydrazine (DMH). The cocarcinogenic effect of cholecystectomy was assumed to be due to an increased production of secondary bile salts by the colonic bacteria and the lack of resorptive function of the gall bladder for some carcinogenic material [366]. Bile salts in the colon introduced by surgical means have been demonstrated in other animal studies to enhance

---

[362] Hecht, S. S., et al. Chemical Studies on Tobacco Smoking Determination of Hydroxybenzyl Alcohols and Hydroxyphenyl Ethanols in Tobacco and Tobacco Smoke. J. Anal. Toxicol., 2(2):56-59, 1978.

[363] DiPaolo, J. A., and P. J. Donovan. *In Vitro* Morphologic Transformation of Syrian Hamster Cells by U.V.-Irradiation is Enhanced by X-Irradiation and Unaffected by Chemical Carcinogens. Int. J. Radiat. Biol., 30(1):41-53, July 1976.

[364] Palotay, J. L., et al. Carcinogen-Induced Cutaneous Neoplasms in Nonhuman Primates. J. Natl. Cancer Inst., 57(6):1269-1274, 1976.

[365] Lohsoonthron, P. The Epidemiologic Study of Subsite Large Bowel Cancer. Diss. Abstr. Int. (B), 36(9):4399-B, 1976.

[366] Werner, B., et al. Cholecystectomy and Carcinoma of the Colon, An Experimental Study. Z. Krebsforsch., 88(3):223-230, 1977.

the carcinogenic effect of substances such as azoxymethane [367, 368]. Other substances present in the large bowel of man have been tested in animal models for their cofactor activity. Bile acids such as cholic acid, chenodroxycholic acid, and lithocholic acid were tested on rats with the carcinogen MNNG and indicated that primary bile acids modified to secondary bile acids by intestinal bacteria exert a strong promoting effect in colon cancer [369]. These same bile acids along with neutral sterols acted as inhibitory agents to B(a)P induced skin tumors on mice [339]. Fecal samples of patients with colon cancer have shown large amounts of bile acids, cholesterol metabolites, high fecal bacterial 7-alpha-dehydroxylase and cholesterol dehydrogenase activity [370]. The chemical fluid, adenosine 3',5'-cyclic monophosphate, is found in all living cells and is essential for muscular action. This substance has been found to enhance skin carcinogenesis by 7,12-dimethylbenzanthracene [371].

Previous findings that trauma is a potential cocarcinogen was supported by two cases of women who developed breast cancer in old thoractomy scars. In each case the combination of scar tissue and surgical trauma seemed significant in the development of cancer [372]. It has also been reported that chronic inflammation can be a cocarcinogenic factor in the formation of bone cancer [373].

---

[367] Williamson, R. C., et al. The Effect of Pancreatobiliary Diversion on Testical Carcinogenesis (Meeting Abstract). Br. J. Surg., 64(11):837, 1977.

[368] Reddy, B. S. Role of Bile Metabolites in Colon Carcinogenesis. Cancer (Suppl.), 36:2401-2406, 1975.

[369] Reddy, B. S., et al. Promoting Effect of Bile Acids on Colon Carcinogenesis in Germfree and Conventional Rats (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:119, 1977.

[370] Wynder, E. L. Metabolic Epidemiology of Colon Cancer. Amer. Health Foundation, Inc., New York, New York.

[371] Curtis, G. L., et al. Enhancement of 7,12-Dimethylbenzanthracene Skin Carcinogenesis by Adenosine, 3',5'-Cyclic Monophosphate. Cancer Res., 34(9):2192-2195, 1974.

[372] Freund, H., et al. Breast Cancer Arising in Thoracotomy Scars (Letter to Editor). Lancet, 1(7950):97, 1976.

[373] Glaser, A. Pathologic and Clinical Aspects of Bone Tumors. Zentralbl. Chir., 101(6):321-329, 1976.

In a survey of lung cancer patients who smoked, chronic bronchitis was shown to be cocarcinogenic with cigarette smoke [374]. In a study of the mechanism of action of polycyclic aromatic hydrocarbon carcinogens it was suggested that antibodies to the carcinogen may enhance the tumorigenicity of the carcinogen [375]. The effects of chronic mechanical irritation of the gastric mucous membrane on stomach carcinogenesis was investigated. It was concluded that foreign bodies had promotive effects in glandular stomach carcinogenesis by MNNG, possibly by prolonging retention of the carcinogen and in turn the exposure to the gastric mucous membrane [376].

Tests conducted in Russia on the effect of magnetic fields on rats concluded that magnetic fields enhanced tumor growth initiated by B(a)P or polyvinyl chloride (PVC) [377]. It has also been reported that rotary motion causes stress which stimulates the functioning of the pituitary glad or adrenal cortex, thus promoting tumor development [378].

THERAPEUTIC AGENTS AND TREATMENTS

Tests have shown that several therapeutic agents exhibit carcinogenic cofactor activity. It is most ironic that certain cancer therapy drugs have been found to be carcinogenic as well as therapeutic in experimental systems. An example of this is actinomycin D which can act as a cancer therapy drug, anticarcinogen, and carcinogen [379]. Other cancer therapy drugs also act as cocarcinogens and augment the tumorigenicity of chemical carcinogens. Clinical studies suggesting an increased incidence of malignant neoplasms in patients with Hodgkin's disease treated intensively with radiation and chemotherapy prompted testing on animals. Test results indicated that procarbazine and ionizing radiation have a synergistic carcinogenic action [380].

---

[374] Lung Cancer and Chronic Bronchitis. Med. M. Aust., 51(24): 926-927, 1964.

[375] Stenback, F., and G. Curtis. Mechanism of Action of Polycyclic Hydrocarbon Carcinogens: Immunological Aspects (Meeting Abstract). Scand. J. Immunol., 6(11):1196, 1977.

[376] Fukushima, S., et al. Effects of Foreign Bodies on Gastric Carcinogenesis in Rats Treated with n-Methyl-n'-nitro-n-nitrosoguanidine (MNNG). (Proc. Jpn. Cancer Assoc., 33rd Annual Meeting, October 1974.) Gann, 67, 1975.

[377] Kogan, A. K. H., and V. I. Kulitskaia. The Effect of a Stationary Magnetic Field on Induced Carcinogenesis. Patol. Fiziol. Eksp. Ter., (2):63-68, 1977.

[378] Suzuki, S. Effect of Rotary Motion on Carcinogenesis. J. Nagoya City Univ. Med. Assoc., 19(4):1517-1558, 1969.

[379] Harris, C. C. The Carcinogenicity of Anticancer Drugs: A Hazard in Man. Cancer, 37(2):1014-1023, 1976.

Other tests with urethan, an antileukemic drug, demonstrated its behavior as both a carcinogenic and cocarcinogenic agent [344, 381]. Melphalan (L-phenylalanine mustard), a cytostatic drug used in the treatment of breast cancer, markedly enhanced mammary tumor formation in mice [382]. Results of tests on allopurinol, used in the treatment of gout and human neoplasia, demonstrate its enhancement potential of bladder cancer in rats induced by N[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) [383]. Data from several cancer centers indicate that immunosuppressive drugs (in transplant recipients) may also act as cocarcinogens with UV light in the induction of skin cancer [384].

Griseofulvin, an antifungal antibiotic, acted as a cocarcinogen with skin applications of 3-methylcholanthrene in mice but not with B(a)P [385]. In a similar study griseofulvin was found to inhibit skin tumors promoted by croton oil and induced by B(a)P but lacked promoting activity by itself [386].

Cignolin, used in the treatment of psoriasis, was tested on mouse skin pretreated with a carcinogenic agent (DMBA or tar). The application of cignolin promoted the formation of skin tumors in more than one-third of the animals tested [387].

---

[380] Arseneau, J. C., et al. Synergistic Carcinogenic Effect of Procarbazine and Ionizing Radiation in CDF Mice. Proc. Am. Assoc. Cancer Res., 16:120, 1975.

[381] Kosir, A. Contribution of Carcinogenesis. Acta Med. Iugosl., 16(2):172-180, 1962.

[382] Medina, D. Enhancement of Mammary Tumor Formation in Mice by a Cytostatic Drug, Melphalan. Cancer Res., 38(1):317-319, 1977.

[383] Want, C. Y., and S. Hayashide. Enchancement of N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT Carcinogenicity for Rat Urinary Bladder by Allopurinol. Proc. Am. Assoc. Cancer Res., 17:149, 1976.

[384] Maize, J. C. Skin Cancer in Immunosuppressed Patients. JAMA, 237(17):1857-1858, 1977.

[385] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 10, 1976. pp. 153-161.

[386] Vesselinovitch, S. D., and N. Mihailovich. The Inhibitory Effect of Griseofulvin on the "Promotion" of Skin Carcinogenesis. Cancer Res., 28(12):2463-2465, 1968.

Animal studies employing the sedative phenobarbital have demonstrated that it can act as a carcinogenic inhibitor or enhancing agent. Phenobarbital given together with diethylnitrosoamine (DENA) reduced the severity of liver carcinogenesis but when administered after DENA it enhanced carcinogenesis [388]. Phenobarbital also enhanced azo-dye induced liver carcinogenesis in rats [389] while inhibiting 4-(dimethylamino)azobenzene induced carcinogenesis [322].

Steroidal anti-inflammatory agents have been tested on mouse skin and have been found to inhibit skin carcinogenesis. Dexamethasone and fluocinolone were the most effective inhibitors while estradiol, estrone, estriol, testosterone and progesterone were found to act as inhibitors but to a lesser degress [390, 391]. Steroidal compounds have also been tested for their cofactor activity in other human applications.

Estradiol dipropionate, an estrogenic compounds, was tested on rabbits with the carcinogen methylcholanthrene, and the results suggest that estrogen may promote uterine cancer [392]. Similar studies with estrogenic compounds and prolactin suggest a synergistic effect on formation of rat mammary tumors [393-395] and a synergistic effect on cervical carcinomas induced by 3-methylcholanthrene (MCA) [396]. However, other researchers, although recognizing that estrone and estradiol are linked to carcinogenicity and cocarcinogenicity, feel that estrogen levels in oral contraceptives are too low to affect genital carcinoma and do not elevate the risk of breast cancer [397]. Another study performed on rats gives evidence to support the concept that sustained elevation of estriol in body fluids inhibits breast carcinogenesis [398].

---

[387] Langbein, W. Contribution to the Cocancerogenic Effect of Cignolin in Animals. Radiobiol. Radiother. (Berl.), 13(2):233-240, 1972.

[388] Weisburger, J. H., et al. Modification of Diethylnitrosoamine Liver Carcinogenesis with Phenobarbital but Not with Immunosuppression. J. Natl. Cancer Inst., 54(5):1185-1188, 1975.

[389] Kitagawa, T., and H. Sugano. Enhancement of Azo-Dye Hepatocarcinogenesis with Dietary Phenobarbital in Rats. Gann, 68(2):255-256, 1977.

[390] Van Duuren, B. L. Tumor-Promoting and Cocarcinogenic Agents in Chemical Carcinogenesis. In: Chemical Carcinogens, Searle, C. E., ed., American Chemical Society Monograph 1973, American Chemical Society, Washington, D.C., 1976. pp. 24-51.

[391] Slaga, T. J., et al. Mechanism of Action of Steroidal Anti-Inflammatory Agents that Inhibit Skin Carcinogenesis. Proc. Am. Assoc. Cancer Res., 16:37, 1975.

[392] Kawaguchi, K. Studies on Experimental Induction of Endometrial Carcinoma in Rabbits, Especially Related to Their Carcinogenesis (Meeting Abstract). Acta Obstet. Gynaecol. Jpn., 21(1):68, 1976.

Enovid, a mammary growth promoting agent, is made up of 98.5% norethynodrel and 1.5% mestranol. Tests conducted with this substance on rats sugget that it may inhibit the carcinogenic induction of mammary tumors but may enhance the growth of tumors already present [399]. Based on medical histories of two women it was suggested that liver cancer may be caused by a synergistic effect of estrogen and progesterone [400].

---

[393] Muhlbock, O., and L. M. Boot. The Mode of Action of Ovarian Hormones in the Induction of Mammary Cancer in Mice. Biochem. Pharmacol., 16(4):627-630, 1967.

[394] Warren, S., and O. Gates. Radiation Carcinogenesis, Progress Report IV, 15 March 1976 - 15 May 1977. Available through National Technical Information Service, Springfield, VA, as C00-3017-31, EY-76-S-02-3017, 1977. 15 pp.

[395] Lee, C., et al. *In Vitro* Interaction of Estrogen and Prolactin on Hormone-Dependent Rat Mammary Tumors. Proc. Soc. Exp. Biol. Med., 148(1):224-226, 1975.

[396] Forsberg, J. G., and L. S. Breistein. A Synergistic Effect of Oestradiol and Prolactin Influencing the Incidence of 3-Methylcholanthrene Induced Cervical Carcinomas in Mice. Acta Pathol. Microbiol. Scand (A), 84(5):384-390, 1976.

[397] Vorherr, H. Contraception Postabortion and Postpartum, Advantages and Disadvantages of Hormonal Contraceptive with Particular Reference to the Relationship Between Female Sex Hormones and Thromboembolism and Carcinoma of the Breast and Genitals. Gynaekol. Rundsch., 15(1):48-73, 1975.

[398] Lemon, H. M. Estriol and Prevention of Mammary Carcinoma. Cancer Detec. Prevent., 1(2):263-281, 1976.

[399] Welsch, C. W. Effects of a Norethynodrel-Mestranol Combination (ENOVID) on Development and Growth of Carcinogen-Induced Mammary Tumors in Female Rats. Cancer, 23(3):601-607, 1969.

[400] Chevrel, B. Role of Steroid Hormones in the Development of Malignant Tumors (Letter to Editor). Nouv. Presse. Med., 5(17):1145, 1976.

Several adrenergic agents have been tested on animals for their cofactor effect. Noradrenaline and atropin were found to enhance liver cancer while isoprenalin inhibited it [401].

ENVIRONMENTAL COFACTORS

Cigarette smoke is an important environmental constituent containing many components which exhibit carcinogenic cofactor activity. A series of 21 tobacco smoke components and related compounds were tested for cocarcinogenic activity on mouse skin with B(a)P as the active carcinogen. The results of the tests are summarized in Table B-1.

TABLE B-1. COCARCINOGENESIS EXPERIMENTS: SUMMARY

Cocarcinogenic activity		Inhibitory activity	
Potent	Weak or moderate	Partial	Complete
Catechol	Benzo(*ghi*)perylene	Phenol	Esculin
Pyrogallol	Lauryl alcohol	Eugenol	Quercetin
Decane	Tetradecane	Resorcinol	Squalene
Undecane		Hexadecane	Oleic acid
Pyrene		Hydroquinone	
B[e]P		Limonene	
Fluoranthene			

Six of the 21 compounds were also tested as tumor promoters in two-stage carcinogenesis. No direct correlation was found between tumor promoting activity and cocarcinogenic activity. The cocarcinogens pyrogallol and catechol did not show tumor promoting activity, while decane, tetradecane, anthralin, and phorbol myristate acetate showed both types of activity [212]. In addition, tumor promoting or cocarcinogenic activity has been attributed to other compounds isolated from cigarette smoke including alkyl naphthalenes and nitrosoamines [402, 403].

---

[401] Gurkalo, B. L., and M. A. Zabezhinsky. Modification of Chemical Carcinogenesis with Adrenergic Compounds. Vestn. Akad, Med. Nauk SSSR, (2):38-42, 1978.

These findings are important because many of the above substances are also contacted by man through either industrial pollution or natural sources (food, etc.).

Another study was undertaken to examine the effect of nicotine on the carcinogenic activity of cigarette smoke condensate on mouse skin. Early in the experiment the largest administered dose of nicotine appeared to inhibit tumor formation. However, at 37 weeks the results demonstrated that low to moderate concentrations of nicotine act as important cocarcinogenic stimuli [404].

Another important potential environmental factor is human viruses. A study of nasopharyngeal carcinoma in Southeast Asia has suggested an undefined cocarcinogenic role for Epstein-Barr virus [405]. Cocarcinogenic activity of viruses was also suggested in a study of hamster tumors. Primary tumors grafted to new animals showed malignant characteristics not present in the original tumors. The malignant potential of the cells could be correlated with the presence of viral particles acting as cocarcinogens [406]. Further studies have been conducted to specifically investigate the cocarcinogenic activity of viruses. On one test human embryo lung cells were infected with oncornavirus LPV and then treated with the carcinogen MNNG. It was concluded that a synergistic effect existed between MNNG and the oncogenic virus [407]. Another significant finding in the area of cocarcinogenic viruses

---

[402] Schmeltz, I., et al. Formation and Determination of Naphthalenes in Cigarette Smoke. Anal. Chem., 48(4):645-650, 1976.

[403] Argus, M. F., and J. C. Arcos. Hydrocarbon-Nitrosoamine Synergism as a Possible Amplying Factor in Lung Turmorigenesis by Tobacco Smoke. J. Theor. Biol., 56(2):491-498, 1976.

[404] Bock, F. G. Cocarcinogenic Activity of Nicotine. Proc. Am. Assoc. Cancer Res., 17:2, 1976.

[405] Etiology of Nasopharyngeal Carcinoma. Lancet, 2(8000):1393, 1976.

[406] DeMicco-Pagis, C., et al. Pathologic and Ultrastructural Investigation of a DMBA-Induced Transplantable Melanoma in the Golden Hamster. Bull Cancer (Paris), 63(1):73-86, 1976.

[407] Stepanova, L. G., et al. DNA Reparation and Chromosome Aberrations in Human Cells Infected with LPV Oncornavirus. Vopr. Virusol., (6):712-716, 1977.

was observed when mice, after successive infections with three mouse-adopted strains of influenza and exposure to ozonized gasoline aerosol, developed lung cancer [408].

INDUSTRIAL CHEMICALS AND POLLUTANTS

There is not a clear distinction between industrial chemicals and industrial pollutants because in most cases the chemicals produced and used by industry may also be discharged to the environment. Tests on rats have suggested a synergistic effect between inhaled vinyl chloride (the monomer used in producing polyvinyl chloride) and ingested alcohol in tumorigenesis [359].

There has been some concern over the solvents employed in testing carcinogens as to their potential cofactor effect. Many of these solvents are also industrial chemicals, and the findings of test programs may also relate to industrial exposure. Benzene, toluene, and acetone were tested in this regard and it was concluded that benzene and toluene have cocarcinogenic potency while acetone had no effect [409]. Acetone has been reported by others as cocarcinogenic [4].

Other solvents which have been tested include decalin, n-dodecane, and 1-dodecanol. In these tests n-dodecane, decalin and 1-dodecanol were found to be cocarcinogenic solvents depending on the concentration of the carcinogenic materials used [B(a)P and benzanthracene] [410]. It has also been reported that the use of n-dodecane as a solvent for B(a)P can result in a 1,000-fold enhancement of the effective concentration of B(a)P for skin tumor induction [341]. Other studies confirm the cocarcinogenic properties of these materials, including n-decane and tetradecane with B(a)P and UV light [411, 412].

---

[408] Bryan, W. R. Current Concepts of Viral Neoplasia. South. Med. J., 57(11):1263-1267, 1964.

[409] Mazzucco, K. The Effect of Various Solvents (Benzene, Toluene, Acetone) Used with Carcinogens on the Collagen Content of the Mouse Dorsal Skin. Osterr. Z. Onkol., 2(2-3):49-51, 1975.

[410] Bingham, E., and H. L. Falk. Environmental Carcinogens, The Modifying Effect of Cocarcinogens on the Threshold Response. Arch. Environ. Health, 19(6):779-783, 1969.

[411] Bingham, E., and P. J. Nord. Cocarcinogenic Effects of n-Alkanes and Ultraviolet Light on Mice. J. Natl. Cancer inst., 58(4):1099-1101, 1977.

[412] Tanaka, T. Influence of n-Dodecane on Rats Exposed Transplacentially to Benzo(a)pyrene and Nitrosomethylurethan During Pregnancy (Meeting Abstract). Third International Symposium on Detection and Prevention of Cancer, 1976. pp. 286-287.

A mineral oil (Drakeol 6VR) was analyzed and consisted of three major components, one containing promoters (e.g., hexadecane), another containing mainly inhibitors, and the third containing both promoters and inhibitors [413]. Carbon tetrachloride, a widely used solvent (e.g., cleaning, fire extinguishers), has been tested on rats and is suspected of acting as a cocarcinogen in formation of liver tumors [414].

Total phenols from waste waters of a shale processing plant applied to mouse skin after a subcarcinogenic dose of B(a)P resulted in development of malignant neoplasms [415]. Others have also reported the cocarcinogenic activity of phenols and anthralin (1,8,9-anthracenetriol) used in the textile industry [344, 416, 417]. Investigation into the frequency of cancers in an aldehyde factory suggest that there may be a syncarcinogenic effect between some aliphatic aldehydes (which are also present in automobile exhaust and cigarette smoke) and some air pollutants [418].

Because dodecylbenzene has been reported to be a cocarcinogen and tumor promoter [341, 419] a group of Russian scientists have tested Sulfonol NP-1, a surfactant made from dodecylbenzene sulfonate, for its potential cocarcinogenicity. Sulfonol NP-1, a mixture of sodium salts of alkylbenzene sulfonic acids, sodium sulfate, and nonsulfonated organic compounds, acted as a cocarcinogen but did not exhibit carcinogenic properties [420]. Another surface-active agent, olefine sulphate, has been tested and demonstrated to enhance B(a)P induced skin cancer [421].

---

[413] Horton, A. W. Cellular Mechanisms of Chemical Carcinogenesis. National Technical Information Service No. PB 225 631, 1973. 91 pp.

[414] Mori, H., et al. Effect of Carbon Tetrachloride on Carcinogenicity of Petasites Japonicus, and Transplantability of Induced Tumors. Gann, 68(6):841-845, 1977.

[415] Mirme, H. Modifying Effect of Water-Soluble Shale Phenols on Carcinogenesis. Vopr. Profil. Zagryaz. Okruzhayushchei. Chel. Sredy Kantserogennymi Veshchestvami; 16-18, 1972.

[416] Hecker, E. Aspects of Cocarcinogenesis. In: Scientific Foundations of Oncology, T. Symington and R. L. Carter, eds., William Heinemann Medical Books, Ltd., Chicago, 1976. pp. 310-318.

[417] Falk, H. L. Possible Mechanisms of Combination Effects in Chemical Carcinogenesis. Oncology, 33(2):77-85, 1976.

[418] Pershagen, G., et al. Mortality in a Region Surrounding an Arsenic Emitting Plant. Environ. Health Perspect., 19:133-137, 1977.

[419] Gargus, J. L., et al. Utilization of Newborn Mice in the Bioassay of Chemical Carcinogens. Toxicol. Appl. Pharmacol., 15(3):552-559, 1969.

The flame retardants tetrakis(hydroxymethyl)phosphonium chloride (THPC) and Pyroset TKP (mixed acetate/phosphate of same phosphonium base) have been tested on mouse skin and found to be active as tumor promoters with DMBA initiation [422]. THPC and Pyroset TKP have been widely used in cotton fabrics, particularly children's sleepware. Other chlorinated compounds found to exhibit cocarcinogenic properties include polychlorinated biphenyls (PCBs) and certain pesticides and herbicides. Chlorophenol pesticides and the herbicide 2,4-D (amine salt of 2,4-dichlorophenoxyacetic acid) were tested on mice and rats and are suggested as potential cocarcinogens [423, 424]. Similar results were obtained from tests on PCB and DDT [425, 426].

As with all agricultural products, pesticides and herbicides, besides being industrial chemicals and pollutants, also result in human exposure during usage and through the food chain. Ammonia, found in many chemical products including fertilizers, has been tested on mouse cells as ammonium salts and a number of primary amines. The evidence implied that ammonia may be carcinogenic or cocarcinogenic [427].

---

[420] Sakharov, I. I., et al. The Cocarcinogenic Activity of Sulfonol NP-1. Gig. Tr. Prof. Zabol., (9):56-58, 1973.

[421] Pyleva, Z. A., et al. Data on the Biological Properties of Olefin Sulfate. Vopr. Onkol., 24(1):55-60, 1978.

[422] Loewengart, G., and B. L. Van Duuren. Evaluation of Chemical Flame Retardants for Carcinogenic Potential. J. Toxicol. Environ. Health, 2(3):539-546, 1977.

[423] Arrhenius, E., et al. Disturbance of Microsomal Detoxication Mechanisms in Liver by Chlorophenol Pesticides. Chem. Biol. Interact., 18(1):35-46, 1977.

[424] Arkhipov, G. N., and I. N. Kozlova. Study of the Carcinogenic Properties of the Herbicide, Amine Salt of 2,4-Dicholorphenoxyacetic Acid. Vopr. Pitan., (5):83-84, 1974.

[425] Uchiyama, M., et al. Cocarcinogenic Effect of DDT and PCB Feeding on Methylcholanthrene-Induced Chemical Carcinogenesis. Bull. Environ. Contam. Toxicol., 12(6):687-693, 1974.

[426] Nagasaki, H., et al. Analysis of Various Factors on Liver Carcinogenesis in Mice Induced by Benzene Hexachloride (BHC) and Technical Polychlorinated Biphenyls (PCBs). J. Nara. Med. Assoc., 25(6):635-648, (Recd. 1975).

Orthophosphate and l-phenylalanine were tested on hamster cheek pouches and found to promote tumor growth. Phenylphosphate, on the other hand, inhibited carcinogenesis [428]. Chromium carbonyl, when tested on rats, was demonstrated to be a carcinogen and acted synergistically with B(a)P [429]. Results of tests with sodium hypochlorite show that it is cocarcinogenic; however, it was concluded that this chemical is not a practical carcinogenic hazard [430]. Repeated application of hydrogen peroxide after application of B(a)P to mouse skin markedly inhibited the carcinogenicity of B(a)P [431].

Other industrial chemicals have been tested and found to be carcinogenic cofactors. Four chemical substances, N-nitrosopiperidine, N-nitrosomorpholine, diethylnitrosoamine, and N-2-fluorenylacetamide) were fed to mice for 4 weeks. Each substance inhibited the induction or urinary bladder cancer by n-butyl-N-(4-hydroxybutyl)nitrosoamine [325]. In tests on oral carcinogens it was found that 2-aminonaphthalene and 4-nitrobiphenyl were very synergistic in the development of bladder cancer in dogs [432]. When two chemicals of the same organotropy (affecting the same organs), such as the liver carcinogens diethylnitrosoamine and 4-dimethylaminoazobenzene, were applied to mice, the effect was synergistic. Syncarcinogenesis was not observed, however, when chemical carcinogens of differing organotropy were tested simultaneously.

---

[427] Capuco, A. V. Amonia: A Modulator of 3T3 Cell Growth. Diss. Abstr. Inst. (B), 38(9):48085, 1978.

[428] Rubin, D., and I. S. Levij. Chemical Carcinogenesis in the Hamster Cheek Pouch: Influence of Inhibitors and Inducers of Alkaline Phosphatase. Pathol. Microbiol. (Basel), 43(1):26-30, 1975.

[429] Lane, B. P., and M. J. Mass. Carcinogenicity and Cocarcinogenicity of Chromium Carbonyl in Heterotopic Tracheal Grafts. Cancer Res., 37(5):1476-1479, 1977.

[430] Hayatsu, H., et al. Potential Cocarcinogenicity of Sodium Hypochlorite. Nature (Lond.), 233(5320):495, 1971.

[431] Nagata, C., et al. Effect of Hydrogen Peroxide, Fenton's Reagent, and Iron Ions on the Carcinogenicity of 3,4-Benzopyrene. Gann, 64(3):277-285, 1973.

[432] Deichmann, W. B., and J. L. Radomski. Synergism Among Oral Carcinogens and Tumorigens, Report of Preliminary Experiments. Toxicol. Appl. Pharmacol., 6(3):343-344, 1964.

Other chemical substances of potential industrial exposure have been investigated through medical histories of people employed in manufacturing operations or exposed to the chemical substance. The lungs of 100 consecutive patients at autopsy and 24 patients with pulmonary neoplasms were analyzed. More than 90% of the patients from both groups had ferruginous (asbestos) bodies in their lungs with no apparent difference in the incidence or quantity between the randomly selected group and those with pulmonary neoplasms. This supports the view that asbestos acts as a cocarcinogen in causing pulmonary neoplasms. These findings also indicate that asbestos dust contamination is widespread throughout rural and urban environments [433].

In a review of toxic challenges to the lung, mention is made of the synergism between quartz and environmental irradiation. However, about tenfold fewer workers with occupationally heavy dust exposure died of bronchial carcinoma than men of equivalent age in the general population [434]. Fibrous glass, whose cancer-causing potential has been established in animal studies, is postulated to act as a cocarcinogen with cigarette smoke and other carcinogens when inhaled [435].

An investigation of chromatid aberrations among smelter employees exposed to arsenic showed a significantly increased frequency in employees versus controls. However, a cocarcinogenic action of arsenic with cigarette smoking was proposed to be responsible for the poor correlation between frequency of aberrations and arsenic exposure [436]. The results of animal testing with arsenic trioxide, metal ore, and refinery flue dust indicated that solid arsenical substances acted cocarcinogenically with B(a)P [437]. Experimental results from exposing rats to beryllium oxide and carbon black with a known carcinogen showed both to be tumor promoters with beryllium being the more potent promoter [438]. Several studies conducted on hamsters have demonstrated that iron oxide (Fe_2O_3) dust enhances chemically induced carcinogenicity [439, 440].

---

[433] Breedin, P. H., and D. H. Buss. Ferruginous (Asbestos) Bodies in the Lungs of Rural Dwellers, Urban Dwellers, and Patients with Pulmonary Neoplasms. South. Med. J., 69(4):401-404, 1976.

[434] Einbrodt, H. J. Combined Effort of Fine Dust on the Lung. Staub Reinhaltung Luft, 36(3):122-126, 1976.

[435] Rom, W. N., and A. M. Langer. Carcinogenicity of Fibrous Glass (Letter to Editor). West. J. Med., 126(5):413, 1977.

[436] Nordenson, I., et al. Occupational and Environmental Risks in and Around a Smelter in Northern Sweden, II. Chomosomal Aberrations in Workers Exposed to Arsenic. Hereditas, 88(1):47-50, 1978.

[437] Ishinishi, N., et al. Preliminary Experimental Study on Carcinogenicity of Arsenic Trioxide in Rat Lung. Environ. Health Perspect., 19:196-196, 1977.

Peracetic acid, perbenzoic acid, and *m*-chloroperbenzoic acid were found to be active tumor promoters in skin carcinogenesis when tested on rats [441]. Pyran copolymer has been tested on mice and found to promote B(a)P induced skin tumors [442].

One of the more important categories of environmental pollution is the area of combustion products. Because combustion operations are widely scattered throughout the population, human exposure cannot be avoided. Sulfur dioxide (SO_2), which is emitted from combustion sources firing sulfur laden fuel (coal, oil), showed significant cocarcinogenic effects with B(a)P, another combustion product, in animal experiments [443].

Studies on trace elements, emitted from most fossil fuel combustion systems, especially coal-fired units, have produced somewhat contradictory results. *In vitro* tests on a series of trace elements indicated that some trace elements have have a cocarcinogenic effect in B(a)P induced cancer [444]. Another study on mice concluded that there was no evidence of trace element cocarcinogenesis with 3-methylcholanthrene [445]. Lead oxide, an emission from automobiles buring leaded gasoline, was tested on hamsters with B(a)P as the carcinogenic substance. Results suggested that lead oxide is a cocarcinogenic material [446]. Lead oxide is also found in and around lead smelters and battery plants.

---

[438] Uzawa, T. Histopathological Studies on Pulmonary Reaction by Beryllium Oxide in Rat (Experimental Tumorous Action of BeO Combined with Carcinogenic Hydrocarbons). Bull. Tokyo Med. Dent. Univ., 9(3):440, 1963.

[439] Nettesheim, P., et al. Carcinogenic and Cocarcinogenic Effects of Inhaled Synthetic Smog and Ferric Oxide Particles. J. Natl. Cancer Inst., 55(1):159-169, 1975.

[440] Sellakumar, A., et al. Effects of Different Dusts on Respiratory Carcinogenesis in Hamsters Induced by Benzo(a)pyrene and Diethylnitrosoamine. Eur. J. Cancer, 12(4): 313-319, 1976.

[441] Bock, F. G., et al. Cocarcinogenic Activity of Peroxy Compounds. J. Natl. Cancer Inst., 55(6):1359-1361, 1975.

[442] Kripke, M. L., and T. Borsos. Accelerated Development of Benzo(a)pyrene-Induced Skin Tumors in Mice Treated with Pyran Copolymer. J. Natl. Cancer Inst., 53(5):1409-1410, 1974.

[443] Shapiro, R. Genetic Effects of Bisulfite (Sulfur Dioxide). Mutat. Res., 39(2):149-176, 1977.

[444] Calop, J., et al. A Study of the Influence of Trace Elements on the Hydroxylation of Benzo(a)pyrene. Eur. J. Toxicol. Environ. Hyg., 9(5):271-286, 1976.

Polycyclic hydrocarbons (PCH) are also emitted from most combustion systems. They are products of incomplete combustion and are emitted in greater quantities from the less efficient combustion equipment. A number of compounds in this class of material are considered carcinogenic; this has stimulated studies on the possible cocarcinogenic effect of PCH.

3-Methylcholanthrene (MCA) and dimethylnitrosoamine (DMN) were tested on mice and found to act synergistically, resulting in enhancement of lung cancer and kidney tumors [447]. However, MCA has also been reported to inhibit or prevent tumorigenesis induced by carcinogenic aromatic amines or azo dyes [448]. Nitrosoamines such as diethylnitrosoamine (DEN) and DMN can be formed from nitrous compounds emitted to the atmosphere. These compounds have been tested on mice by others and found to be cocarcinogenic in the lung [449].

Usually considered to be a noncarcinogenic PCH, benzo(e)pyrene [B(e)P] has been reported to act as a cocarcinogen when applied to mouse skin with B(a)P. However, when tested in a respiratory tract tumor model, B(e)P did not act as a cocarcinogen and may have inhibited B(a)P carcinogenicity [450]. Three other PCH carcinogenic compounds [MCA, B(a)P, and DMBA] were tested in subeffective concentrations to determine the synergistic action of any two compounds. All combinations of any two of these compounds exhibited a synergistic action [451].

---

[445] Shimkin, M. G., et al. Lung Tumor Response in Mice to Metals and Metal Salts. Adv. Exp. Med. Biol., 91:85-91, 1977.

[446] Kobayashi, N., and T. Okamoto. Effects of Lead Oxide on the Induction of Lung Tumors in Syrian Hamsters. J. Natl. Cancer Inst., 52(5):1605-1610, 1974.

[447] Cardesa, A., et al. The Syncarcinogenic Effect of Methylcholanthrene and Dimethylnitrosoamine in Swiss Mice. Z. Krebsforsch., 79(2):98-107, 1973.

[448] Danz, M., et al. Prevention of 2-Acetylaminofluorene-Induced Extrahepatic Short-Term Effects by 3-Methylcholanthrene. Exp. Pathol. (Jena), 13(4-5):262-267, 1977.

[449] Cardesa, A., et al. Effects of Intraperitoneal Injections of Dimethyl- and Diethylnitrosoamine, Alone or Simultaneously on Swiss Mice. Z. Krebsforsch., 82(3):233-238, 1974.

[450] Topping, D. C., et al. The Interaction of Benzo(a)pyrene and Benzo(e)pyrene in Respiratory Tract Carcinogenesis (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 19:43, 1978.

Ozone, a secondary pollutant, results from the photo-oxidation of primary combustion pollutants such as nitrogen oxides and hydrocarbons. Tests on hamsters exposed to ozone followed by B(a)P resulted in B(a)P induced lung cancer with ozone acting as a cocarcinogen [452]. The cofactor effects of industrial chemicals and pollutants are summarized in Table B-2.

ESOTERIC MATERIALS AND OTHER SUBSTANCES

Several substances have been found that act as carcinogenic cofactors, but they have little or no potential for human exposure and are employed mainly as research substances. A prime example is croton oil which has been found to be a strong promoter and can be relied upon to exhibit promoting properties when studying cancer mechanisms or substances suspected of initiating carcinogenesis. Croton oil, a plant extract (Euphorbiaceae), has been reported to act mainly as a promoter [344, 453] but has also been reported as a cocarcinogen [345]. Possibly the difference is actually caused by a misuse in terminology.

Several other studies have reported substances related to the Euphorbiaceae plant family that also acted as promoters or cocarcinogens. Latex samples from a plant in this family showed toxic and cocarcinogenic activity traceable to a palmitic acid ester of a polyfunctional diterpene [454]. A followup study confirmed the cocarcinogenic activity of diterpene esters of Euphorbiaceae [455]. TPA (12-O-tetradecanoylphorbol-13-acetate), sometimes referred to as PMA (phorbol myristate acetate), is also a substance from the Euphorbiaceae family which has been reported

---

[451] Mondal, S., et al. Syncarcinogenesis in Culture C3H/10T½ Cells (Meeting Abstract). Proc. Am. Assoc. Cancer Res., 18:8, 1977.

[452] Palmer, M. S., et al. Effect of Ozone on Benzpyrene Hydroxylase Activity in the Syrian Golden Hamster. Cancer Res., 31(6):730-733, 1971.

[453] Sellakumar, A. R., et al. Influence of Croton Oil in Hamster Lung Carcinogenesis. Proc. Am. Assoc. Cancer Res., 16:57, 1975.

[454] Hecker, E. Cocarcinogenic Agents Derived from Euphorbiaceae. Planta. Med., 1968:24-25, 1968.

[455] Hecker, E. New Toxic, Irritant, and Cocarcinogenic Diterpene Esters from Euphorbiaceae and from Thymelaeceae. Pure Appl. Chem., 59(9):1423-1431, 1977.

TABLE B-2. INDUSTRIAL CARCINOGENIC COFACTORS AND THEIR EFFECTS WITH SOLITARY CARCINOGENS

Cofactor	Cofactor effect				Solitary carcinogen or initiator
	Promoter	Cocarcinogen	Syncarcinogen	Inhibitor	
Asbestos		X			Environmental carcinogens
Quartz			X		Environmental irradiation
Fibrous glass		X			Cigarette smoke
Arsenic		X			Cigarette smoke, benzo(a)pyrene [B(a)P]
Beryllium oxide	X				20-Methylcholanthrene
Carbon black	X				20-Methylcholanthrene
Iron oxide			X		B(a)P, diethylnitrosoamine
Peracetic acid	X				(Known carcinogen)
Perbenzoic acid	X				(Known carcinogen)
m-Chloroperbenzoic acid	X				(Known carcinogen)
Sulfur dioxide		X			B(a)P
Ozone		X			B(a)P
Trace elements		X			B(a)P
Lead oxide		X			B(a)P
3-Methycholanthrene			X		Dimethylnitrosoamine
3-Methylocholanthrene				X	Azo dyes, aromatic amines
Benzo(e)pyrene		X			B(a)P (skin)
Benzo(e)pyrene				X	B(a)P (respiratory tract)

(continued)

TABLE B-2 (continued).

Cofactor	Cofactor effect				Solitary carcinogen or initiator
	Promoter	Cocarcinogen	Syncarcinogen	Inhibitor	
Pyran copolymer	X				B(a)P
Vinyl chloride			X		Ingested alcohol
Benzene		X			(Known carcinogen)
Toluene		X			(Known carcinogen)
Acetone		X			Polycyclic aromatic hydrocarbons
Decalin		X			B(a)P, benzanthracene
n-Dodecane		X			B(a)P, benzanthracene, UV light
1-dodecanol		X			B(a)P, benzanthracene
n-Decane		X			UV light
n-Tetradecane		X			UV light
Mineral oil (Drakeol 6VR)	X			X	(Known carcinogen)
Carbon tetrachloride		X			Petasite japonicus
Phenols		X			B(a)P
Anthralin		X			(Known carcinogen)
Aliphatic aldehydes			X		Air pollutants
Dodecylbenzene		X			(Known carcinogen)
Sulfonol NP-1		X			3-Methylcholanthrene
Olefine sulfate			X		B(a)P

(continued)

TABLE B-2 (continued).

Cofactor	Cofactor effect				Solitary carcinogen or initiator
	Promoter	Cocarcinogen	Syncarcinogen	Inhibitor	
Tetrakis(hydroxymethyl)-phosphonium chloride	X				7,12-Dimethylbenz(a)anthracene
Pyroset-TKP	X				7,12-Dimethylbenz(a)anthracene
Polychlorinated biphenyls		X			Benzene hexachloride, methylcholanthrene
Chlorophenol		X			(Known carcinogen)
2,4-D herbicide		X			(Known carcinogen)
DDT pesticide					Methylcholanthrene
Ammonium compound		X			(Known carcinogen)
Orthophosphate	X				9,10-Dimethyl-1,2-benzanthracene
1-Phenylalanine	X				9,10-Dimethyl-1,2-benzanthracene
Phenylphosphate				X	9,10-Dimethyl-1,2-benzanthracene
Chromium carbonyl			X		B(a)P
Sodium hypochlorite		X			4-Nitroquinoline-1-oxide
Hydrogen peroxide				X	B(a)P
N-nitrosopiperidine				X	n-Butyl-N-(4-hydroxybutyl)nitrosoamine
N-nitrosomorpholine				X	n-Butyl-N-(4-hydroxybutyl)nitrosoamine
Diethylnitrosoamine				X	n-Butyl-N-(4-hydroxybutyl)nitrosoamine
N-2-fluorenylacetamide				X	n-Butyl-N-(4-hydroxybutyl)nitrosoamine
2-Aminonaphthalene			X		4-Nitrobiphenyl
4-Dimethylaminoazobenzene			X		Diethylnitrosoamine

to be cocarcinogenic [456-458]. Phorbol is the parent dieterpene of TPA and is not cocarcinogenic [459].

Other reported promoters and cocarcinogens of unknown signifcance, as far as potential human exposure, include 4-ethylsulfonylnaphthalene-1-sulfonamide (promoter) [344], and n-butyl-N-(4-hydroxybutyl)nitrosoamine, N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide, and 3,3'-dichlorobenzidine (cocarcinogens) [460]. Inhibitors of unknown origin and unknown human significant include alpha-naphthylisothiocyanate, *p*-hydroxypropiophenone [323], *cis*-aconetic acid, putrescine [461], and elipticine [462].

---

[456] zor Hausen, H. Z., et al. Persisting Oncogenic Herpesvirus Induced by the Tumour Promoter TPA. Nature (Lond.), 272(5651):373-375, 1978.

[457] Komitowski, D., et al. Epidermal Intercellular Relationships During Carcinogenesis and Cocarcinogenesis as Revealed by Scanning Electron Microscopy. Virchows Arch. (Cell Pathol.), 24(4):317-333, 1977.

[458] Janoff, A., et al. Local Vascular Changes Induced by the Cocarcinogen, Phorbol Myristate Acetate. Cancer Res., 30(10):2567-2571, 1970.

[459] Soper, C. J., and F. J. Evans. Investigations into the Mode of Action of the Cocarcinogen 12-O-Tetradecanoylphorbol-13-acetate Using Auxotrophic Bacteria. Cancer Res., 37(8, Part 1):2487-2491, 1977.

[460] Tsuda, H., et al. Synergistic Effect of Urinary Bladder Carcinogenesis in Rats Treated With n-Butyl-N-(4-hydroxybutyl)nitrosoamine, n-[4-(5-Nitro-2-furyl)-2-thiazolyl]-formamide, n-2-Fluorenylacetamide, and 3,3'-Dichlorobenzidine. Gann, 68(2):183-192, 1977.

[461] Kallistratos, G. Prevention of 3,4-Benzpyrene Carcinogenesis by Naturally Occurring and Synthetic Compounds. Meunch. Med. Wochenschr., 117(10):391-394, 1975.

[462] Truhart, R., et al. Inhibitor Effect of Ellipticine [Dimethyl-5, II-(6H) Pyrido (4,3-B Carbazole) on Rat Liver Carcinogenesis Induced by BT6 (n,n-Dimethyl-*p*-benzothiazolylazo) Aniline]: Incidences on Cytochrome P450 and Arginase Activity (Meeting Abstract). Fourth Meeting of the European Association for Cancer Research (held at Universite de Lyon, September 13-15, 1977), European Association for Cancer Research, Lyon, France, 1977. p. 86.